American Journal of Ophthalmology Case Reports 38 (2025) 102319

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Coexistence of congenital lacrimal gland agenesis and congenital aniridia: Case report

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ARTICLE INFO

Keywords:
Aniridia
Dry eye
Lacrimal gland agenesis

ABSTRACT

Purpose: To document a rare case of congenital aniridia due to paired box gene 6 (PAX6), elongated protein 4 (ELP4) and fusion gene DKFZp686k1684 mutation with bilateral congenital lacrimal gland agenesis and multiple ocular comorbidities, aiming to expand the understanding of its clinical presentations and therapeutic interventions.

Observations: A 10-year-old female presented with severe dry eyes and photophobia, with no tears since birth in both eyes. Diagnosed with sporadic aniridia, previously the patient developed secondary glaucoma requiring multiple surgeries in both eyes. Examination revealed severe dry eyes, foveal hypoplasia, aniridia-associated keratopathy, and was suspicious for absence of lacrimal gland with no palpebral lobe evident on bilateral external inspection. Magnetic resonance imaging revealed lacrimal gland hypoplasia of the right eye and lacrimal gland agenesis of the left eye. Over 10 years, the patients' condition was managed with punctal plugs and artificial tears allowing for stable vision with resolution of bilateral superficial punctate keratitis. Whole genome sequence analysis revealed a large deletion in chromosome 11p13 including the whole PAX6 gene, ELP4 and fusion gene DKFZp686k1684.

Conclusion and importance: This case illustrates an association between congenital aniridia and lacrimal gland agenesis. The findings highlight the complexity of genetic influences on ocular development and the importance of early identification and management to prevent complications.

1. Introduction

Classic congenital aniridia (Online Mendelian Inheritance in Man identifier, OMIM, 106210) was first described in 1918 by Barrata.[1] It is a pan-ocular condition that manifests mainly as a range of iris hypoplasia associated with abnormalities affecting both the anterior and posterior segments of the eye.[2]A heterozygous mutation in the paired box gene 6 (*PAX6*; OMIM *607108; 11p13), accounts for approximately two-thirds of the cases, while the remaining cases are sporadic. Sporadic aniridia carries a relative risk of 67 (with a confidence interval of 8.1–241) for developing a significant chromosomal deletion at 11p13, leading to WAGR (Wilms tumor, aniridia, genitourinary anomalies, and range of developmental delays) syndrome (OMIM *194072), a potentially life-threatening condition.[3] Other associated systemic manifestations in aniridia, like in Gillespie syndrome, can include intellectual disability as well as cerebellar and pineal gland hypoplasia.[4] Lately, other non PAX6 genetic mutations in genes such as FOXC1, PITX2, CYP1B1, and FOXD3 can result in both partial and complete aniridia phenotypes. The TRIM44 gene has been demonstrated to be linked with total aniridia.[5,6]

Although the most distinguishing ocular manifestation is iris hypoplasia, which has minimal effect on the vison, other ocular associations such as foveal hypoplasia, aniridia-associated keratopathy (AAK) with features of limbal stem cell deficiency (LSCD), cataract, glaucoma and dry eye disease (DED) contribute greatly to visual impairment.[2,7] DED is a common comorbidity in aniridia, affecting 56 %–95 % of individuals.[9] DED is a multifactorial disease resulting from poor tear film quality and/or production.[8] In anidiria, DED primarily results from LSCD, poor tear film quality and meibomian gland dysfunction.[10] Lacrimal gland agenesis has not been previously reported in aniridia, however, theoretically any loss of tear production by the lacrimal gland could contribute greatly to the increased severity of DED, especially in these patients.[8] Herein, we present a unique case of a patient exhibiting

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https://doi.org/10.1016/j.ajoc.2025.102319
Received 13 July 2024; Received in revised form 6 March 2025; Accepted 17 March 2025
Available online 22 March 2025

congenital aniridia in conjunction with congenital lacrimal gland hypoplasia and agenesis.

2. Case report

A 10-year-old female was referred to the oculoplastic service due to severe DED and bilateral photophobia. The parents reported the absence of tears since birth even when the child cries. At the age of two months, she was diagnosed to have sporadic aniridia with unremarkable family history of similar condition nor any systemic association. Screening with serial abdominal ultrasound was initiated for Wilms tumor since that age. The patient developed secondary glaucoma in both eyes at the age of seven years, necessitating multiple surgical interventions including trabeculectomy and deep sclerectomy with mitomycin C in both eyes due to un-controlled intraocular pressure (IOP). On examination, best corrected visual acuity (BCVA) was 20/160 in the right eye and 20/300 in the left eye. IOP was 12 mmHg in the right eye and 13 mmHg in the left eye without glaucoma eye drops. Slit-lamp examination showed nystagmus, patent lower eyelid puncta, +1 inferior conjunctival hyperemia, corneal punctate epithelial keratitis, a clear cornea centrally with LSCD stage IA(less than 180° conjunctival invasion not extending to central cornea), and aniridia in both eyes(Fig. 1). The lens showed an early posterior subcapsular cataract (PSC) in the right eye and a central anterior capsular cataract with +1 PSC in the left eye. Schirmer I test result was two and zero in the right and left eye respectively at 5 minutes. Fundus exam showed a tessellated fundus appearance, pale glaucomatous optic neuropathy, and foveal hypoplasia with thinned retina and choroid on optical coherence tomography in both eyes (Fig. 2). Orbital magnetic resonance imaging (MRI) demonstrated a myopic configuration of both globes with posterior staphyloma and markedly hypoplastic right lacrimal gland, accompanied by absence of lacrimal gland tissue in the left lacrimal fossa (Fig. 3). Goldmann visual field revealed central island bilateral. The child was diagnosed with severe dry eye secondary to congenital lacrimal gland hypoplasia and agenesis respectively, in the right and left eyes. Bilateral punctal plugs in the upper and lower eyelids were inserted with the addition of topical artificial tears and lubricating ointment. At her last office visit, the patient was clinically comfortable with stable vision and improved corneal status with the resolution of both eyes superficial punctate keratitis. Whole genome sequence analysis revealed a large deletion in chromosome 11p13 including the whole PAX6 gene, ELP4 and fusion gene DKFZp686k1684. Both parents genetic test yielded wild type PAX6 gene confirming sporadic inheritance.

3. Discussion

This case report illustrates the unique coexistence of congenital aniridia and congenital lacrimal gland hypoplasia and agenesis, an association that expands our understanding of the phenotypic spectrum associated with aniridia. In addition to glaucoma, AAK is a significant contributor to progressive vision loss in aniridia.[11] Around 80 % of patients with congenital aniridia develop AAK during their first decade of life.[12,13] Patients with severe AAK, DED, LSCD and ocular surface exposure are at high chance of failure if they need to have advanced corneal surgery such as corneal transplant and Keratoprosthesis (KPro). The identification of this condition and medical management are vital to prevent early graft failure.[9,11]

Congenital aniridia is commonly associated with mutations in the PAX6 gene (the master regulator of the eye) which has more than 500 mutations resulting in different clinical phenotypical presentation.[14,15] Recent studies demonstrate that the PAX6 gene and its cis-regulatory region ectodermal enhancer play an important role in lacrimal gland development.[16,17] Nevertheless, other non PAX6 genetic mutations were linked to congenital aniridia and their full role in the contribution of lacrimal gland development is yet to be fully understood. A recent study on organoids from human lacrimal glands highlighted the future possibility of lacrimal gland transplantation as well as the critical role PAX6 plays in differentiating lacrimal gland cells.[18,19] Congenital lacrimal gland hypoplasia and agenesis have never been reported as an association with ELP4 and fusion gene DKFZp686k1684 mutation, as seen in our patient.

Other congenital conditions related to lacrimal gland agenesis/hypoplasia are listed in (Table 1).[20–25] The findings underscore the complexity of PAX6 and potentially other genetic influences in ocular development, pointing to a broader genetic basis that could affect multiple ocular structures including the lacrimal gland. Our patient's journey over a decade highlights the critical challenges in managing such complex cases, particularly the control of secondary glaucoma and the management of LSCD, keratopathy and secondary severe DED, which are crucial to preserving visual function and improving quality of life.

4. Conclusion

This case illustrates an association between congenital aniridia due to PAX6, ELP4 and fusion gene DKFZp686k1684 mutation and lacrimal gland hypoplasia and agenesis in aniridia. The findings highlight the complexity of genetic influences on ocular development. The identification of this condition is vital to contribute to the medical management of corneal surfaces and in extreme cases of LSCD, preventing failure of advanced corneal surgeries.

CRediT authorship contribution statement

Khawlah A. Alzaben: Writing – original draft, Investigation. **Bayan S. Alshuhayb:** Writing – original draft. **Sulaiman M. Alsulaiman:**

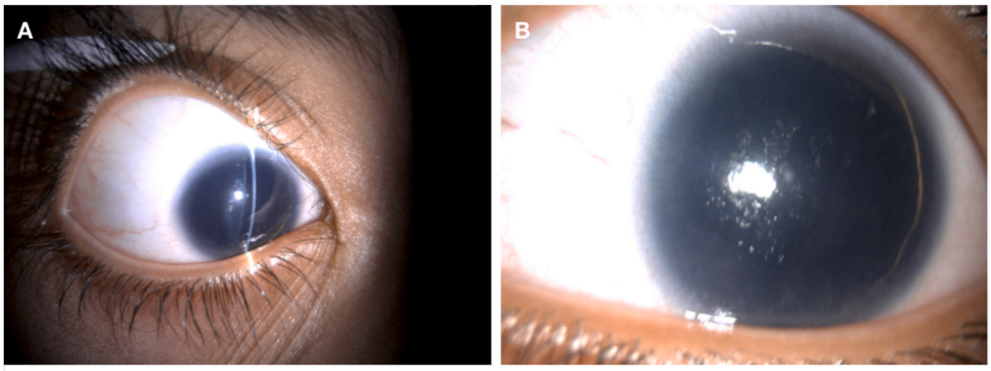

Fig. 1. Slit lamp photographs of bilateral congenital aniridia in the (A) right eye and (B) left eye, light reflex highlighting the corneal status with severe dry eye disease.

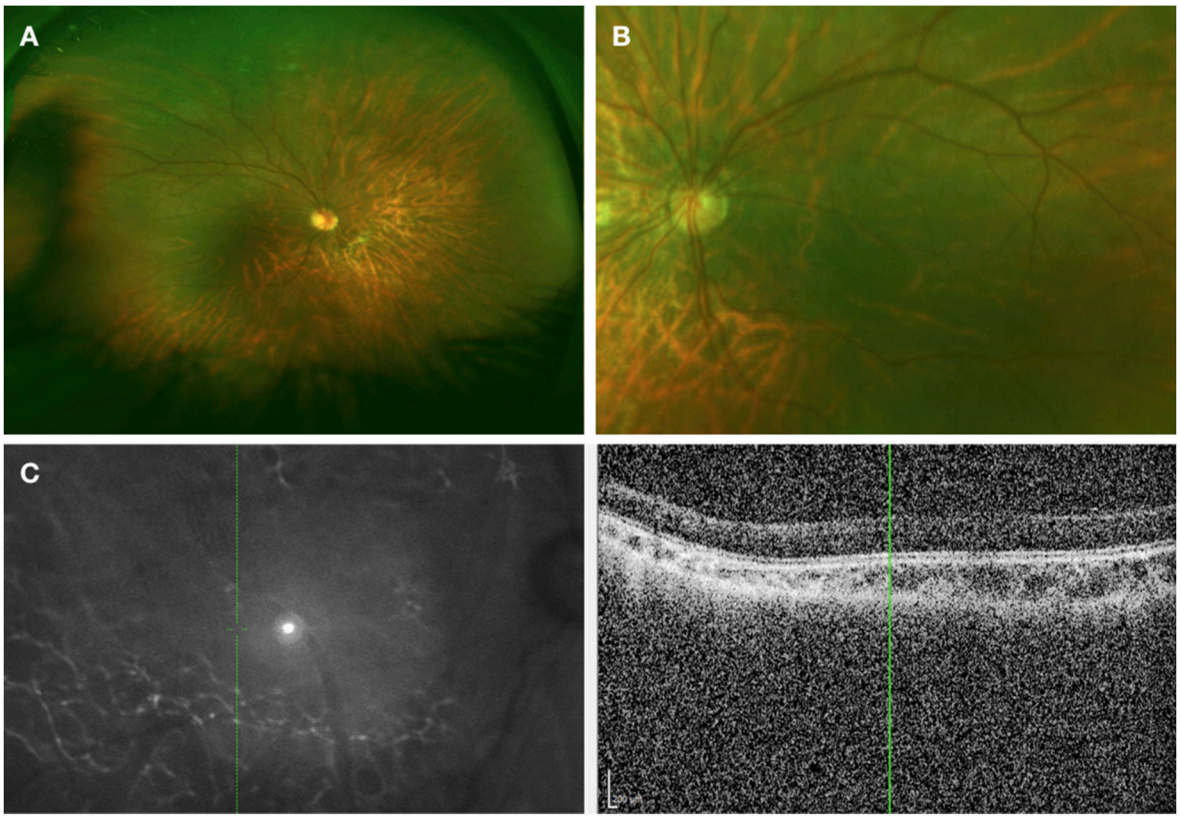

Fig. 2. Bilateral tessellated fundus appearance, glaucomatous optic neuropathy, and foveal hypoplasia in the (A) right eye and (B) left eye, thinned retina, choroid and foveal hypoplasia on optical coherence tomography of the right eye, notable artifact due to cataract(C).

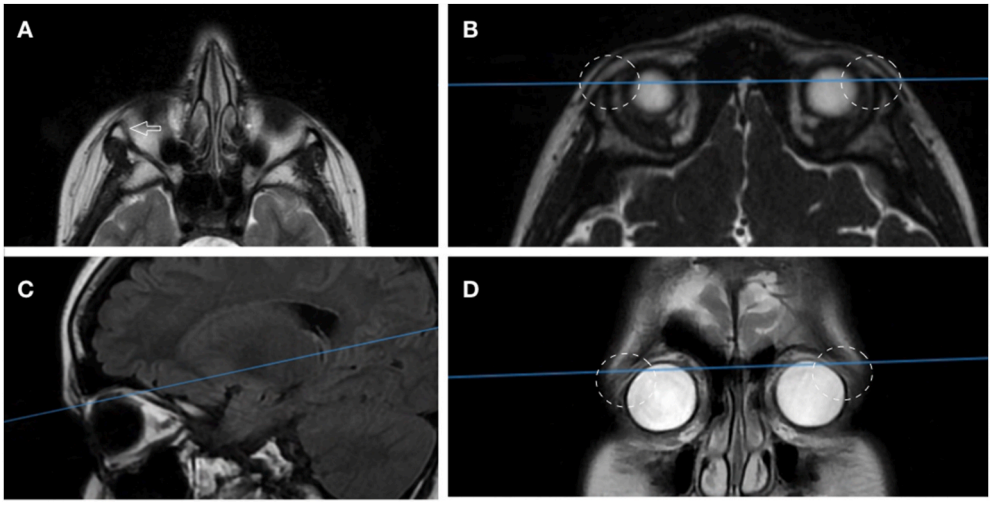

Fig. 3. Delineation of empty lacrimal gland fossa on magnetic resonance imaging (MRI) on T2 Fat Suppressed FIESTA (Fast Imaging Employing STeady-state Acquisition) MRI sequence, "white arrow" highlighting marked hypoplasia of the right lacrimal gland(A). Empty lacrimal fossa "dotted circle" of the same level "blue line" on different MRI sequence, axial (B), sagittal T2 FLAIR (Fluid-attenuated inversion recovery) (C), coronal T2 PROPELLER (Periodically Rotated Overlapping ParallEL Lines with Enhanced Reconstruction) (D). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Writing – review & editing, Supervision. **Maram Alenazi:** Writing – review & editing. **Mashael A. Alkhayyal:** Writing – review & editing, Supervision.

Patient consent

The patient consented to the publication of the case.

Approval by the Institutional Review Board at King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia was obtained.

Claims of priority statement

After conducting a literature review on October 25, 2024, utilizing PubMed, Google Scholar, and Cochrane Library, Scopus, and Web of

Table 1
Summary of different congenital disorders associated with lacrimal gland agenesis/hypoplasia.

Phenotype	Location	OMIM Number	Inheritance	Gene/ Locus	Clinical features
Blepharophimosis, epicanthus inversus, and ptosis, type 1	3q22.3	110100	AD, AR	FOXL2	Ptosis, epicanthus inversus, and telecanthus.
Blepharophimosis, epicanthus inversus, and ptosis, type 2	3q22.3	110100	AD, AR	FOXL2	Ptosis, epicanthus inversus, and telecanthus.
Aplasia of lacrimal and salivary glands	5p12	180920	AD	FGF10	Aplasia/hypoplasia of salivary glands.
LADD syndrome 1	10q26.13	149730	AD	FGFR2	Aplasia/hypoplasia of salivary glands, dental, digital, ear anomalies, deafness.
Craniofacial microsomia	11q13.1	164210	AD	SF3B2	Hemifacial microsomia.
Frontonasal dysplasia 2	11p11.2	613451	AR	ALX4	Skull defects, alopecia, encephalocele, hypertelorism, wide nasal bridge, notched nose, depressed nasal tip.
PCWH syndrome	22q13.1	609136	AD	SOX10	Neurologic involvement Hirschsprung disease, deafness, iris heterochromia, hypomelanic skin patches.

AD, autosomal dominant; **ALX4**, Aristaless-like homeobox 4; **AR**, autosomal recessive; **FGFR2**, Fibroblast growth factor receptor 2; **FGF10**, Fibroblast growth factor 10; **FOXL2**, Forkhead box protein L2; **LADD**, Lacrimo-auriculo-dento-digital; **OMIM,** Online Mendelian Inheritance in Man; **PCWH**, Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease; **SF3B2**, Splicing factor 3B subunit 2; **SOX10**, SRY-Box Transcription Factor 10.

Science using the key words "congenital lacrimal gland agenesis," "congenital aniridia," and "lacrimal gland anomalies with aniridia," we did not find any prior reports of Coexistence of Congenital Lacrimal Gland Agenesis and Congenital Aniridia.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Funding

No funding or grant support.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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