Keratoconus in Axenfeld Rieger Syndrome Patient: Dysgenesis or Dystrophy

Hilary L Boyer, BA, BS, MID, Thuy – Lan Nguyen OD, FAAO, FSLS, Stacy Zubkousky, OD, FAAO, FSLS

Nova Southeastern University, College of Optometry, Fort Lauderdale, Florida

Background

Keratoconus and Axenfeld-Rieger syndrome are seemingly distinct eye conditions that do not have a well-established association. Keratoconus (KCN) is the most common corneal dystrophy with links to almost 100 ocular and systemic diseases.[1] It both thins and steepens the cornea, leading to irregular corneal shape and reduced vision. [1] Although the mechanisms behind KCN are poorly understood, evidence suggests that it is multifactorial with a genetic component.[1] Axenfeld Rieger syndrome (ARS) is a rare genetic disorder caused by mutations. [2] The resulting dysgenesis involving neural crest cells affects the development of eyes, teeth, and facial structures. [2] Notable anterior segment abnormalities include posterior embryotoxon, iris hypoplasia, corectopia, and polycoria. [2]

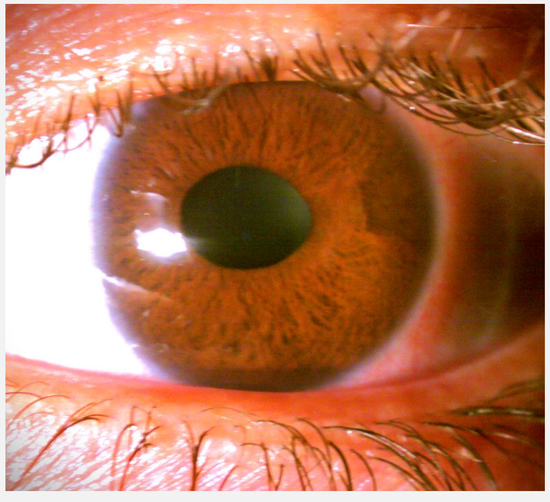


Figure 1 & 2: Anterior segment photos: 31-year-old with female with ARS. Temporal aspect of iris hypoplasia causing horizontally elongated corectopia. Observed OU.

Case Report

A 31-year-old female presented to The Eye Care Institute at NSU for a contact lens examination and comprehensive eye exam. Her ocular history is positive for ARS and KCN OD and OS. Her family history revealed her mother and brother both have ARS and KCN. Her medical history is positive for dental hypoplasia with dental implants, stomach surgery, and GI obstruction. She reported her mother's genetic testing had indicated *PITX2* as the causative gene.

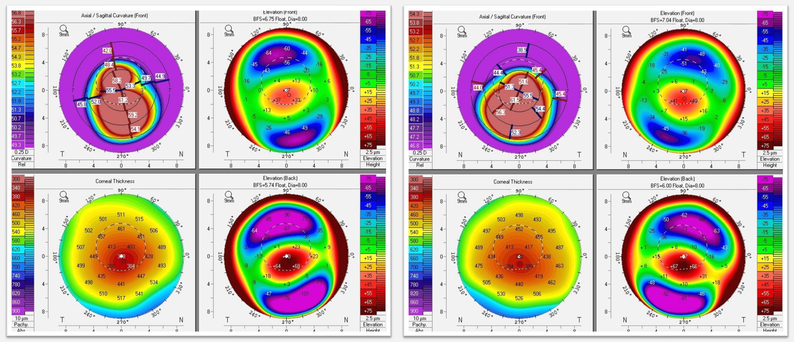
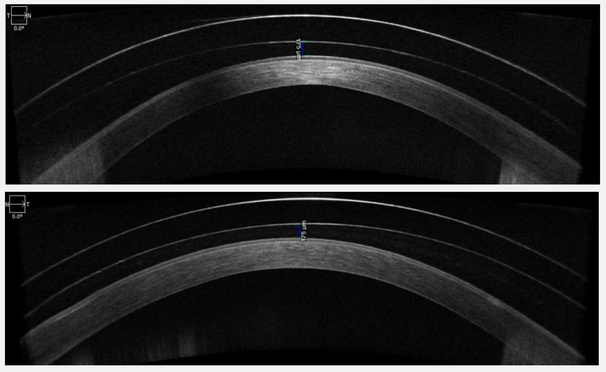


Figure 3 & 4: Refractive maps of 31-year-old female OD and OS show distinctly keratoconic corneas.

Manifest refraction was OD: -15.25 -6.00 x 030 and OS: -13.75 -4.50 x125 with best corrected acuities of 20/125 and 20/60 respectively. Her physical examination revealed posterior embryotoxon with iris strands, corectopia of the pupils, iris hypoplasia temporal to the pupil. The patient topography showed advanced keratoconus in both eyes, her steep K's 59.9D OD and her 56.2D OS. Both elevation maps showed central steeping, with pachymetry measurements of 374 OD and 384 OS at the thinnest point. She was fit with a One Fit Med Scleral gas permeable lenses with a BCVA of 20/20 OU.

Blachard One Fit Med in Optimum Extra with plasma
OD: -1.25 / 4200 Sag / 15.6 OAD / Std M / Std L / +100/-50 E / 0.24 CT /Clear with dot
OS: -2.00 / 4200 Sag / 15.6 OAD / Std M / Std L / +100/-50 E / 0.28 CT / Blue no dot



Figures 5 & 6: Anterior segment photos of a 31-year-old female fit with scleral lens. Central clearance of 175um OU, with increased clearance temporally. Corneal thickness is closer to that of the scleral lenses than that of a normal cornea.

Discussion

Systemic conditions most associated with keratoconus include atopy, down's syndrome, and connective tissue disorders.[1] Metanalysis of KCN research reveals that the pathogenesis in these conditions is still not fully understood.[1] In rare diseases, like ARS, research is more limited to small populations and case studies. By understanding both the genetic nature of ARS and the embryologic development of the anterior segment, it becomes clear that the development of KCN in ARS patients is logical, despite the enigmatic nature of most keratoconus cases.

ARS is caused by mutations within transcription factors genes utilized by neural crest cells during embryonic development.[2] Up to 70% of ARS cases have been linked to either *PITX2* or *FOXC1*.[3] *PITX2* linked cases of ARS have been shown to display an increased amount of iris hypoplasia and cranial facial abnormalities.[2] Corneal stroma and endothelium, iris stroma and muscles, ciliary body stroma, trabecular meshwork, and sclera are all derived from neural crest cells.[2] Mutations in the genes responsible for these tissues results in structure and functionality variations as seen in ARS.[2]

Conclusion

Although, Axenfeld Rieger syndrome has not been well associated with keratoconus, this case demonstrates distinct genetic involvement. The very nature of dysgenesis, arising from neural crest cells is indicative of a corneal stromal abnormality. Corneal stromal abnormalities are likely to lead to stromal dystrophies, such as keratoconus. This is especially true in cases of ARS where the corneas may be excessively thin or weaken, with poor drainage and high risk for glaucoma. Performing corneal topography on all ARS patients, especially those with *PITX2*, would increase detection of KCN in more patients.

References

1. Unni P, Lee HJ. Systemic Associations with Keratoconus. *Life (Basel)*. 2023;13(6):1363.
2. Michels K, Bohnsack BL. Ophthalmological Manifestations of Axenfeld-Rieger Syndrome: Current Perspectives. *Clin Ophthalmol*. 2023;17:819-828.
3. Zamora EA, Salini B. Axenfeld-Rieger Syndrome. StatPearls –NCBI bookshelf 2022.