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## Keratoconus in a patient with Alport syndrome: A case report

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### Abstract

#### BACKGROUND

Known ocular manifestations of Alport syndrome include features such as anterior lenticonus and fleck retinopathy. Reports of keratoconus in such patients are limited. We report tomographic findings consistent with keratoconus in a patient with Alport syndrome.

#### CASE SUMMARY

A 52-year-old female was referred to our ophthalmology clinic with decreased vision and increased tearing. She was diagnosed with stage III Alport syndrome two years prior. Upon examination she was found to have average keratometries of 48 D bilaterally with tomographic evidence of keratoconus.

#### CONCLUSION

Although a rare presentation, concurrent Alport syndrome and keratoconus should be considered when reviewing the ocular health of Alport syndrome patients and appropriate management steps should be taken upon the diagnosis.

**Key words:** Alport syndrome; Keratoconus; Type IV collagen; COL4A genes; Corneal ectasia; Case report

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**Core Tip:** Various ocular manifestations of Alport syndrome have been well described. However, reports of keratoconus in the presence of Alport syndrome is limited in the literature. Keratoconus is a form of corneal ectasia and has shown disorganized and thinning collagen under microscopy. Both Alport syndrome and keratoconus demonstrate collagenous changes which may eventually lead to impaired function of the affected tissue. We present a case of keratoconus in the presence of Alport syndrome.

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## INTRODUCTION

Alport syndrome is an inherited disease characterized by progressive renal disease, hearing loss, and ocular abnormalities. It was first described as “familial congenital haemorrhagic nephritis” by Arthur Cecil Alport in 1927<sup>[1]</sup>. Inherited genetic mutations of *COL4A5* (X-linked), *COL4A3* and *COL4A4* (autosomal recessive) produce defects in the alpha chains that form type IV collagen<sup>[2,3]</sup>. Type IV collagen is a component of basement membranes throughout the body<sup>[4]</sup>. Specifically, the heterotrimer *α3α4α5* plays a crucial role in the glomerular basement membrane of the kidney, stria vascularis of the cochlea, Descemet’s membrane and Bowman’s layer of the cornea, lens capsule, and both the inner limiting membrane and Bruch’s membrane of the retina<sup>[5]</sup>. The most common ocular manifestations in Alport patients are corneal opacities, anterior lenticonus, cataract, fleck retinopathies, and temporal retinal thinning<sup>[5]</sup>. The prevalence of the disease has been estimated around 1:10000 with the X-linked variant accounting for 85% of the disease<sup>[6]</sup>.

Keratoconus is a corneal dystrophy resulting in corneal ectasia due to central or paracentral stromal thinning<sup>[7]</sup>. The pathophysiology is poorly understood, but breaks in Bowman’s layer, collagen disorganization, and scarring have all been described. Although the etiology remains unknown, both genetic and environmental factors, such as eye rubbing, are believed to contribute to the disease process. Keratoconus has a known association with Down syndrome, Leber’s congenital amaurosis, and connective tissue diseases such as Ehler’s Danlos<sup>[8]</sup>.

Despite the wide variety of ocular manifestations found in patients with Alport syndrome, corneal ectasia appears to be a rare finding. The literature is limited on the presence of keratoconus in these patients<sup>[9]</sup>. We report an interesting case of tomographic findings consistent with keratoconus in a patient with Alport syndrome.

## CASE PRESENTATION

### Chief complaints

A 52-year-old female was referred to our ophthalmology clinic with decreased vision and increased tearing.

### History of present illness

She was diagnosed with stage III Alport syndrome two years prior which was currently stable per her nephrologist. During these two years had gradual decline in her visual acuity that was not correctable to 20/20.

### History of past illness

She had a past medical history of asthma, diabetes mellitus, and hypertension.

### Family history

Family history was positive for Alport syndrome in her mother and brother but without any known ocular or hearing abnormalities.

### Physical examination

On initial examination (Table 1), uncorrected distance visual acuity was 20/60 on the right and 20/30 on the left, with a corrected visual acuity of 20/30 bilaterally.

**Table 1** Parameters from the patient's initial and follow-up encounters

Encounter	Initial encounter	2 mo follow up	Initial encounter	2 mo follow up
Eye	OD	OD	OS	OS
Vision Acuity				
UDVA	20/60 <sup>c</sup>	20/60	20/30 <sup>c</sup>	20/40
BCVA	20/30	20/25-2	20/30	20/25+
Man. Refraction	-1.50-1.75 x 031	-0.75-2.25 x 037	-1.00-2.75 x 149	-0.75-3.75 x 147
Tomography				
Front				
K1 (flat)	47.0 D	46.7 D	47.1 D	47.1 D
K2 (steep)	48.9 D	49.5 D	49.6 D	50.1 D
Km	47.9 D	48.1 D	48.3 D	48.5 D
Axis	31.0°	36.1°	146.4°	148.7°
Back				
K1	-6.5	-6.5	-6.7	-6.7
K2	-6.9	-6.9	-6.9	-7.0
Km	-6.7	-6.7	-6.8	-6.8
Axis	40.3°	53.6°	123.9°	134.2°
Pachymetry				
Pupil center	506 µm	502 µm	474 µm	472 µm
Pachy apex	505 µm	499 µm	472 µm	463 µm
Thinnest	496 µm	489 µm	454 µm	448 µm

UDVA: Uncorrected distance visual acuity; BCVA: Corrected distance visual acuity; Km: Mean keratometry.

Slit lamp examination showed bilateral eyelid laxity, papillary conjunctival changes, prominent nerves, superficial punctate keratitis, unilateral (OD) anterior basement membrane changes, with no guttata, apical scarring, or corneal striae. Dilated fundus exam revealed bilateral floaters in the vitreous humor and normal retinal vasculature.

### Imaging examinations

Initial Pentacam (Oculus, Wetzlar, Germany) tomography revealed mean keratometry of 47.9 D in the right and 48.3 D in the left, with a 2 mo follow-up scan revealing a mean keratometry of 48.1 D and 48.5 D respectively (Table 1). During this 2 mo period progressive corneal thinning occurred bilaterally. There was also bilateral anterior curvature steepening with no appreciable changes in the posterior curvature.

## FINAL DIAGNOSIS

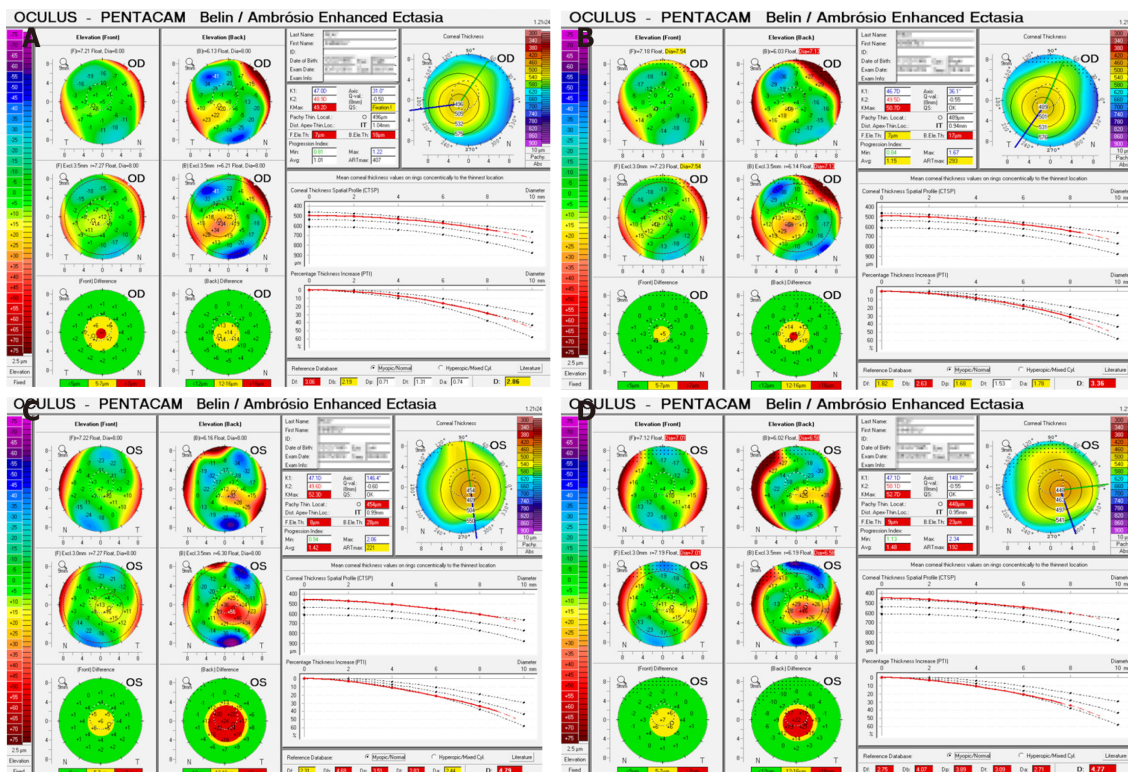
Average keratomeries above 47 to 48 D have been shown to correlate with keratoconus<sup>[10,11]</sup>. Based on the Amsler-Krumeich Classification system our patient was diagnosed with stage 2 keratoconus, with signs of progression over two months, including further corneal thinning and increased steepening of the disease<sup>[12,13]</sup>. This diagnosis was reinforced with the Pentacam Belin/Ambrosio Enhanced Ectasia Display which highlights tomographic abnormalities consistent with keratoconus (Figure 1).

## TREATMENT

Although no curative treatment is available for patients with Alport syndrome, Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone inhibitors reduce stress on the kidneys and may slow the progression of renal failure<sup>[14,15]</sup>. Yearly hearing and vision tests are recommended for patients diagnosed with Alport syndrome from the time the patient is 7 or 8 years old<sup>[14]</sup>.

Ophthalmologic manifestations of Alport syndrome are treated symptomatically, including lens removal and intraocular lens placement for lenticonus and cataract. Our patient was advised to continue to use glasses and avoid eye rubbing.





**Figure 1** Pentacam Belin/Ambrosio enhanced ectasia display highlighting abnormal values of deviation of front elevation difference map, deviation of back elevation difference map, deviation of average pachymetric progression, deviation of minimum thickness, deviation of Ambrosio relational thickness (ART max), and total deviation. A: Initial examination of right eye; B: 2 Mo follow-up of right eye; C: Initial examination of left eye; D: 2-Mo follow-up of left eye. Df: Deviation of front; Db: Deviation of back; Dp: Deviation of average pachymetric; Dt: Deviation of minimum thickness; Da: Deviation of Ambrosio; D: Total deviation.

## OUTCOME AND FOLLOW-UP

While her keratoconus was mild, continued signs of disease progression would warrant discussion of corneal collagen crosslinking while reserving corneal transplantation for advanced disease.

## DISCUSSION

The concurrent presentation of Alport syndrome and keratoconus, to our knowledge, has only been described once in the literature. Chugh *et al*<sup>[9]</sup> reported that 3 of 45 (6.7%) patients diagnosed with Alport syndrome were found to have associated keratoconus. This is the first report in the literature of tomographic findings consistent with keratoconus in a patient with Alport syndrome. While the inheritance patterns for Alport syndrome are well defined, the inheritance of keratoconus is under much investigation. Variants of the COL4A3 and COL4A4 genes are two of many possible genetic causes of keratoconus<sup>[16-18]</sup>. One study found that seven polymorphisms of COL4A3 and COL4A4 were associated with keratoconus, although no mutations were directly linked with the disease<sup>[17]</sup>. A meta-analysis of genetic associations for keratoconus concluded that COL4A4 had differential effects on keratoconus between ethnic groups<sup>[18]</sup>. Specific mutations of the COL4A3 and COL4A4 genes are known to cause of Alport syndrome.

A range of kidney-related diseases including chronic renal failure, kidney transplant, hypertension, diabetes mellitus, and various medications have been associated with keratoconus<sup>[19]</sup>. One theory is that both renal and ocular tissues express the PAX6 gene. PAX6 is linked to corneal gelatinase B, which is a metalloprotease responsible for corneal structure regulation. Thus, a mutated PAX6 gene may contribute to keratoconus and renal pathology<sup>[19]</sup>. Aldave *et al*<sup>[20]</sup> reported cases of polymorphous corneal dystrophy (PPCD) in Alport patients<sup>[5]</sup>. However, the process of corneal steepening found in PPCD is likely independent from that found in keratoconus, as the steepening often presents with the absence of other clinical features of keratoconus.

In Alport syndrome, the normal collagen IV  $\alpha3\alpha4\alpha5$  network is lost and the

immature  $\alpha1\alpha1\alpha2$  network persists. This  $\alpha1\alpha1\alpha2$  network has fewer crosslinks and more proteolytic cleavage sites. This produces basement membranes that are more susceptible to biomechanical strain. It also induces an increase in matrix metalloprotease activity<sup>[5]</sup>. Increased activity of protease enzymes and decreased protease inhibitors have been found in keratoconus<sup>[11]</sup>. Disorganization of collagen fibrils and a diminished number of crosslinks within and between such fibrils contributes to the weakened biomechanical state of the cornea in keratoconus<sup>[21]</sup>. Increased protease activity and decreased crosslinking may be a possible connection between the two diseases.

Further studies are necessary to elucidate the underlying molecular mechanisms possibly linking keratoconus and Alport syndrome. One of the limitations of this report is an absence of genetic testing. We were unable to obtain sequencing and analysis of the patient's exome or genome. These tests would have the potential to reveal specific genetic mutations leading to Alport syndrome in this patient and a more definitive link to keratoconus. When obtained, these tests will provide much value.

## CONCLUSION

Although a rare presentation, concurrent Alport syndrome and keratoconus should be considered when reviewing the ocular health of Alport syndrome patients and appropriate management steps should be taken upon the diagnosis.

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