Ocular Features in Alport Syndrome: Pathogenesis and Clinical Significance

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Abstract
Alport syndrome is an inherited disease characterized by progressive renal failure, hearing loss, and ocular abnormalities. Mutations in the COL4A5 (X-linked), or COL4A3 and COL4A4 (autosomal recessive) genes result in absence of the collagen IV α3α4α5 network from the basement membranes of the cornea, lens capsule, and retina and are associated with corneal opacities, anterior lenticonus, fleck retinopathy, and temporal retinal thinning. Typically, these features do not affect vision or, in the case of lenticonus, are correctable. In contrast, the rarer ophthalmic complications of posterior polymorphous corneal dystrophy, giant macular hole, and maculopathy all produce visual loss. Many of the ocular features of Alport syndrome are common, easily recognizable, and thus, helpful diagnostically, and in identifying the likelihood of early-onset renal failure. Lenticonus and central fleck retinopathy strongly suggest the diagnosis of Alport syndrome and are associated with renal failure before the age of 30 years, in males with X-linked disease. Sometimes, ophthalmic features suggest the mode of inheritance. A peripheral retinopathy in the mother of a male with hematuria suggests X-linked inheritance, and central retinopathy or lenticonus in a female means that recessive disease is likely. Ocular examination, retinal photography, and optical coherence tomography are widely available, safe, fast, inexpensive, and acceptable to patients. Ocular examination is particularly helpful in the diagnosis of Alport syndrome when genetic testing is not readily available or the results are inconclusive. It also detects complications, such as macular hole, for which new treatments are emerging.

Introduction
Alport syndrome is characterized by hematuria, progressive renal failure, hearing loss, and ocular abnormalities affecting the cornea, lens, and retina (1,2). Corneal scarring, temporal retinal thinning, giant macular hole, and maculopathy are recently described features that extend the ophthalmic phenotype (Figures 1–3) (3–7).

Alport syndrome affects at least one in 10,000 individuals, and the diagnosis is important because of the risk of disease in other family members; also, early treatment with angiotsin-converting enzyme inhibitors delays the onset of end stage renal failure (8,9).

Inheritance of Alport syndrome is X-linked in nearly all families (85%), and mutations affect the COL4A5 gene, which codes for the collagen IV α5-chain (10,11). The diagnosis of X-linked Alport syndrome is often overlooked, especially in women, who are affected three times as often as men. Inheritance in the other 15% of Alport families is autosomal recessive with homozygous or compound heterozygous mutations in trans in the COL4A3 or COL4A4 gene, which corresponds to the collagen IV α3- or α4-chain (12,13). The occurrence of an autosomal dominant form of Alport syndrome is controversial. Thin basement membrane nephropathy represents the carrier state for autosomal recessive Alport syndrome, and affected individuals have a heterozygous COL4A3 or COL4A4 mutation (13,14) but no ocular or other extrarenal abnormalities (15).

The characteristic ocular features of Alport syndrome are corneal opacities, anterior lenticonus and cataract, central perimacular and peripheral coalescing fleck retinopathies, and temporal retinal thinning. Rarely, posterior polymorphous corneal dystrophy, a macular hole, or a maculopathy impacts vision. Lenticonus, corneal dystrophy, central and peripheral fleck retinopathies, temporal retinal thinning, and giant macular hole are all highly suspicious for the diagnosis of Alport syndrome.

Biochemistry of Collagen Type IV
Collagen IV is the most abundant protein found in basement membranes and is responsible for the membrane’s strength and integrity. It also contributes to many biologic functions through its interactions with other proteins and cells (16).

Collagen IV occurs as three heterotrimers (α1α1α2, α3α4α5, and α5α5α6) that form distinct networks (17). Individual chains have an intermediate collagenous sequence with glycine as every third amino acid, because it is the only residue small enough to fit inside the collagen helix. The collagen IV α1α1α2 network predominates in embryonic membranes and the adult vasculature. It is replaced by the α3α4α5 network in the adult glomerulus (glomerular basement membrane), cochlea (stria vascularis), cornea (Descemet’s and Bowman’s membranes) (18), lens capsule, and retina (inner limiting membrane and Bruch’s membrane) (19), and by the α5α5α6 network in the skin (17).
Collagen Mutations

In total, >1200 unique variants have been described in X-linked Alport syndrome (www.LOVD.nl). They are missense (40%), nonsense mutations and complex changes that result in a downstream nonsense change (40%), and splice site mutations (10%) (20). Missense mutations typically produce misfolded proteins that are retained within the endoplasmic reticulum and destroyed by the unfolded protein response (21). Nonsense mutations, such as for other inherited collagen diseases, probably result in nonsense-mediated decay, where most of the corresponding mRNA is degraded (21). Both missense and nonsense COL4 mutations have a positive-negative effect, causing the loss of not only the corresponding collagen chain but also, those with which it normally forms the a3e5 heterotrimer.

The loss of the collagen IV a3e4e5 network and the persistence of the immature a1a1a2 network produce abnormal membranes and the clinical features characteristic of Alport syndrome. The a1a1a2 network is less structurally sound with fewer intra- and interheterotrimer cross-links (22,23) and more proteolytic cleavage sites than the a3e4e5 network (16). It is also more susceptible to biomechanical strain (24), which is exaggerated by the overproduction of ectopic laminin chains (25), and induces matrix metalloproteinase activity (26–28).

Genotype-Phenotype Correlations

In X-linked Alport syndrome, the clinical phenotype depends on both the location of the mutation and the nature of the substituting residue (29–32) (Figure 1). Missense mutations near the carboxy terminus, large rearrangements, insertions and deletions, and nonsense mutations typically result in early-onset renal failure (before the age of 30 years), hearing loss, lenticulons, and retinopathy (29–31). Single-nucleotide substitutions that replace glycine with more highly charged or larger residues (arginine, aspartic, or glutamic acid) also produce a more severe phenotype (32). Missense mutations near the amino terminus usually result in mild disease. A genotype-phenotype correlation is less obvious in females with X-linked Alport syndrome because of the effects of Lyonization (33), but the same rules for phenotype severity appear to apply for autosomal recessive and X-linked inheritance (34).

Cornea: Recurrent Corneal Ulcers, Corneal Clouding, and Posterio Polymorphous Corneal Dystrophy

Corneal disease is recognized infrequently in Alport syndrome. Erosions (3,35) result from an abnormal Bowman’s membrane in the corneal subepithelium (Figure 2A) and posterior polymorphous corneal dystrophy from an abnormal Descemet’s membrane in the subendothelium (Figure 2, B–D). The affected membranes lack the collagen IV a3e4e5 network, are weak, and adhere poorly to the epithelium, endothelium, and underlying stroma (36).

Superficial corneal erosions occur in <10% of patients (3,35) but are intermittent and hence, seem to be less common. Their onset may precede the diagnosis of Alport syndrome and is often in the late teenage years. They typically occur in individuals with early-onset renal failure and extrarenal features. Sometimes, corneal erosions are found in different members of the same family, but they do not appear to be associated with specific mutations.

Erosions are accompanied by episodes of unilateral or bilateral ocular pain occurring spontaneously at night or first thing in the morning, with watering, photophobia, and blurred vision (Figure 2A). Symptoms last 2–5 days and recur (35). Precipitants include working at a computer screen and irritation from the wind or contact lenses. On examination, the eye is red, and there are opacities and vesicles anteriorly at the epithelium on slit-lamp examination (37). Most episodes resolve with supportive measures, such as an eye pad, topical antibiotics, and pain relief, but sometimes, they result in corneal clouding and scars.

Posterior polymorphous corneal dystrophy is rare and more serious than the corneal erosions (Figure 2, B–D) (3,38). Again, patients may be asymptomatic, or complain of recurrent episodes of grittiness, watering, and photophobia. The diagnosis is made when multiple clusters of vesicles (“doughnuts”) or bands (“snail tracks”) are demonstrated at the posterior corneal surface on slit-lamp biomicroscopy or with specular microscopy, in vivo confocal microscopy, or high-resolution anterior segment optical coherence tomography (OCT; OCT
is a little like ultrasound but uses the reflection of light rather than sound from surfaces in the eye to demarcate different layers (39). The vesicles result from vacuolar degeneration of dying cells or multilayered epithelial cell protuberances from Descemet's membrane (40–42). Treatment is usually symptomatic; sometimes, the dystrophy progresses, and corneal transplantation is required.

Corneal erosions are distinguished from posterior polymorphous corneal dystrophy by causing gritty eyes rather than visual loss, being more prevalent, and their location in the anterior cornea.

Lens: Anterior Lenticous and Cataracts

The demonstration of lenticous is diagnostic for Alport syndrome (Figure 3). Anterior lenticous is present in 50% of men, but not women, with X-linked disease, where it is associated with early-onset renal failure and perimacular retinopathy. In contrast, lenticous is common in both men and women with autosomal recessive inheritance, and therefore, women with Alport syndrome and lenticous are likely to have recessive disease (43,44).

Lenticous results from the conical protrusion of the lens anteriorly through the thinnest and weakest part of the capsule (Figure 3B) (45). The absence of the α3ε4ε5 network from the capsule means that it develops partial splits that may rupture (Figure 3C). Cataracts develop from healing of small spontaneous ruptures (46). Lenticous ceases to progress after cataract formation (47). Posterior lenticous also occurs but is less common (48).

Lenticous is often first seen in early middle age after the onset of renal failure. Patients have progressive difficulty in focusing because of their abnormal lens shape. The diagnosis is made when there is an oil droplet sign on direct ophthalmoscopy or slit-lamp examination (Figure 3A). Lenticous worsens until visual symptoms require treatment, and most patients eventually require surgery. Treatment for both symptomatic lenticous and cataract is lens removal and intraocular lens implantation (49). Lenticous does not recur after lens replacement.

Retina: Central Fleck Retinopathy and Peripheral Coalescing Retinopathy

Common retinal abnormalities include central or perimacular fleck retinopathy and peripheral coalescing fleck retinopathy. They also include manifestations of temporal thinning (4), such as loss of the foveal reflex, a lozenge, disturbances of foveal pigmentation (50), including a bull’s eye or vitelliform maculopathy (7), and lamellar and giant macular hole (6,51) (Figure 4, Table 1).

Central fleck retinopathy is present in 60% of men and at least 15% of women with X-linked Alport syndrome and 50% of individuals with recessive disease (Figure 4, A–C) (52). It is more common with early-onset renal failure and lenticous. Nearly all individuals with the central retinopathy also have a peripheral retinopathy, but the converse is not true (53). The central retinopathy varies from scattered whitish-yellow dots and flecks to a dense, almost confluent annulus around the region of temporal retinal thinning. The fleck retinopathy is associated with an abnormal inner limiting membrane (54).

The clear demarcation of the central retinopathy from the foveola is consistent with involvement of the inner limiting membrane/nerve fiber layer. This is not a true membrane but rather, results from fusion of the Muller cell end plates and incorporates the collagen IV α3ε4ε5 network. The central retinopathy probably represents an abnormality of these end plates. Thinning of the inner limiting membrane/nerve fiber layer may interfere with the nutrition of the overlying cells, removal of debris, and maintenance of the watertight barrier.

Visual acuity is essentially normal, although formal testing of retinal function shows minor abnormalities. The central retinopathy is best seen with color photographs and redfree images centered on the macula. Specialized tests of retinal function, such as electroretinogram and electrooculogram, are normal or nearly normal. The central retinopathy becomes more prominent with time. No treatment is required.

The peripheral fleck retinopathy is the most common retinal abnormality, occurring in most men and 25% of women with X-linked Alport syndrome and most individuals with recessive disease (Figure 4, D–F) (53). The peripheral retinopathy is characterized by asymmetric patches of confluent flecks (54). The fleck location in relation to the blood vessels and appearance on OCT suggest that they result mainly from an abnormality at the level of the retinal pigment epithelium/Bruch’s membrane. The finding of a peripheral retinopathy is a very helpful pointer to the diagnosis of Alport syndrome, especially in women with X-linked disease (53).

The peripheral retinopathy is associated with early-onset renal failure, lenticous, and central retinopathy but also occurs in women with X-linked disease who have normal renal function (53). It is probably more common than the central retinopathy because of the periphery’s larger surface area.

Visual acuity is, again, normal. The peripheral retinopathy is best seen on ophthalmic examination or with retinal

Figure 3. | Lens abnormalities. (A) Lenticous appearance on slit-lamp examination showing an anterior dimple or oil droplet (arrow) in a man with X-linked Alport syndrome, renal impairment, and posterior polymorphous corneal dystrophy. The oil droplet is also obvious on direct ophthalmoscopy or slit-lamp examination (Figure 3A). Lenticous worsens until visual symptoms require treatment, and most patients eventually require surgery. Treatment for

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photographs that extend beyond the standard views into the periphery and with redfree retinal images. Again, tests of retinal function are normal (54). No treatment is required.

Temporal Retinal Thinning, Dull Macular Reflex, Lozenge, Foveopathy, and Macular Hole

Temporal retinal thinning is very common in men and women with X-linked Alport syndrome, and with recessive disease (Figure 4, G–J) (4,55). The lozenge (56), dull macular reflex (56,57), foveopathy, and lamellar and macular holes all affect the temporal retina (Figure 4, K–O) (6,51) and reflect retinal thinning of both the inner limiting membrane and Bruch’s membrane (4,19,44).

Temporal thinning is apparent on retinal color photography as the dull macular reflex or lozenge with a larger, more oval shape rather than the normal round foveal reflex. Thinning is confirmed with retinal thickness measurements in the <5th percentile on OCT (55). Although thinning is common in all forms of Alport syndrome and less sensitive diagnostically than a peripheral retinopathy, its demonstration is more objective. Thinning occurs with retinal ischemia but otherwise, not in non-Alport renal failure. Tests of retinal function are normal when there is thinning only. Vision is not affected.

Foveopathy

Hypopigmentation occurs in Alport syndrome but is typically overlooked (58). It is often present together with perimacular flecks or other ocular features. Vision and visual fields are not usually affected. Occasionally, severe forms, such as a bull’s eye or vitelliform retinopathy, are found (7).
Lamellar and Giant Macular Holes

Lamellar or partial-thickness macular holes are uncommon in men with X-linked Alport syndrome and men and women with recessive disease (55). Full-thickness holes are even less common. Macular holes occur at a younger age and are larger (giant holes) than the spontaneous holes in patients who do not have Alport syndrome. Holes may be bilateral, asymmetric, or unilateral. They start with multiple small defects (59) hollowed out from the surface of the inner limiting membrane (6) due to accelerated passage of fluid through the defective Bruch’s membrane, and followed by fusion of the microcysts, when the abnormal membrane breaks down (51). Thus, full-thickness macular holes arise from collagen IV abnormalities in Bruch’s membrane and the internal limiting membrane together with anomalous vitreoretinal traction, retinal detachment (60), and anterior lens capsule rupture (61).

Patients with macular holes have difficulty with central vision and metamorphopsia (where straight lines are distorted). Holes sometimes only become evident when there is no improvement in vision after surgery for lenticonus. Lamellar holes are not necessarily seen on retinal photographs, and OCT is required for their demonstration. They may be confused with a retinal lozenge. Holes in Alport syndrome respond less well to surgical closure and often result in a permanent loss of vision.

Clinical Usefulness of Ophthalmic Features

The ocular features of Alport syndrome are explained by distribution of the collagen IV α3α4α5 network in basement membranes of the eye, mutations that result in the loss of this network, basement membrane thinning, lamellation and rarefaction, and the intraocular mechanical stresses.

Most of the ocular features in Alport syndrome do not affect vision but are useful diagnostically, and in some cases, they suggest the likelihood of early-onset renal failure and the mode of inheritance.

Some ocular features (lenticonus and central and peripheral retinopathy) are common in Alport syndrome, and their presence confirms the diagnosis (Table 2). Retinal temporal thinning is very common and suggests Alport syndrome in an individual with hematuria or renal failure. Posterior polymorphous corneal dystrophy and macular hole are rare but also suggest this diagnosis. Ocular features are less sensitive but more specific than hearing loss in Alport syndrome, because hearing loss occurs with other inherited renal diseases and in dialysis patients.

In addition, ocular features may help distinguish between X-linked and autosomal recessive inheritance. Thus, a peripheral retinopathy in the mother of a boy with hematuria indicates not only the diagnosis of Alport syndrome but also, that inheritance is X-linked. Lenticonus, central retinopathy, and macular hole are rare in women with X-linked disease. Thus, a woman referred for investigation of hematuria who

<table>
<thead>
<tr>
<th>Ocular Feature</th>
<th>X-Linked Alport Syndrome (%)</th>
<th>Autosomal Recessive Alport Syndrome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent corneal erosions</td>
<td>&lt;10</td>
<td>Not described</td>
</tr>
<tr>
<td>Posterior polymorphous corneal dystrophy</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Lenticonus</td>
<td>50</td>
<td>75 (52)</td>
</tr>
<tr>
<td>Central or perimacular fleck retinopathy</td>
<td>70</td>
<td>75 (52)</td>
</tr>
<tr>
<td>Peripheral retinopathy</td>
<td>80</td>
<td>75 (52)</td>
</tr>
<tr>
<td>Temporal retinal thinning</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>Lamellar macular hole</td>
<td>&lt;5</td>
<td>Not described</td>
</tr>
<tr>
<td>Other maculopathies</td>
<td>&lt;5</td>
<td>Not described</td>
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Table 2. Prevalence of ocular features in X-linked and autosomal recessive Alport syndrome

<table>
<thead>
<tr>
<th>Ocular Feature</th>
<th>Diagnostic</th>
<th>Severe Mutations</th>
<th>Early-Onset Renal Failure</th>
<th>Distinguish Autosomal Recessive Alport Syndrome from X-Linked Alport Syndrome in Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior polymorphous corneal dystrophy</td>
<td>Yes (38,40)</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Lenticonus</td>
<td>Yes (50)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (52)</td>
</tr>
<tr>
<td>Central retinopathy</td>
<td>Yes</td>
<td>Yes (31)</td>
<td>Yes (31)</td>
<td>Yes (52)</td>
</tr>
<tr>
<td>Retinal thinning</td>
<td>Yes (55)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Giant macular hole</td>
<td>Yes (51)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Peripheral retinopathy</td>
<td>Yes (54)</td>
<td>No (31)</td>
<td>No</td>
<td>No</td>
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</table>

Table 2. Usefulness of ocular features in diagnosis, predicting early-onset renal failure, and identifying mode of inheritance
has any of these features is likely to have not only Alport syndrome but also, autosomal recessive inheritance.

Some ocular features are associated with early-onset renal failure in X-linked Alport syndrome. Thus, lenticous and central retinopathy usually indicate renal failure onset before the age of 30 years. Early-onset renal failure occurs more often with COL4A5 mutations such as large rearrangements, nonsense mutations, etc. Lenticous and central retinopathy also seem to be more common in autosomal recessive inheritance caused by nonsense mutations (34).

**Which Ocular Investigations Should Be Performed?**

Why are ocular abnormalities in Alport syndrome often overlooked? The classic retinopathy does not affect vision and can be subtle or even confused with a youthful retinal sheen. Ophthalmologists see many minor retinal changes in their routine practice, and, unless vision is abnormal, may not report these.

In assessing patients with possible Alport syndrome, it is important to work closely with an interested ophthalmologist who performs a formal ophthalmic examination with slit-lamp examination as well as retinal photography and OCT. These tests are widely available, inexpensive, noninvasive and acceptable to patients. Corneal abnormalities are best seen on slit-lamp examination. Lenticous appears as a bubble in the red reflex on ophthalmoscopy, although an ophthalmologist will use a retinoscope. The central retinopathy is usually evident on retinal photographs but more obvious with redfree images. The peripheral retinopathy may be obvious on standard retinal views, but peripheral examination may be necessary. OCT demonstrates temporal retinal thinning, especially in men with X-linked disease and individuals with recessive inheritance.

When a boy presents for investigation of Alport syndrome, ocular features are less likely to be present, but his mother should be examined, especially for the peripheral retinopathy.

The recent “Expert Guidelines for the Management of Alport Syndrome and Thin Basement Membrane Nephropathy” recommend that Alport syndrome be diagnosed with genetic testing (62). The finding of any of the ocular features of Alport syndrome, although they rarely interfere with vision, provides additional evidence supporting this request and also, in rare instances, for explaining vision impairment.

**Acknowledgments**

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**Disclosures**

None.

**References**
