

## Alport's syndrome

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### Abstract

Alport's syndrome (Haemorrhagic Familial Nephritis) is a rare syndrome. It encompasses a group of heterogeneously inherited disorders involving the basement membrane of the kidney frequently involving the cochlea and the eye. We describe here the detailed ocular findings and the systemic problems of a case of Alport's syndrome in a 30 years male from Nepal. The current understanding of the clinical features and aetiopathogenesis are also discussed.

**Key words:** Alport's syndrome, Anterior lenticonus, Oil droplet sign, Anterior capsular cataract, Perimacular flecks

In 1927, Alport first described the combination of progressive hereditary nephritis with sensorineural deafness. The presence of 3 of the following 4 proposed diagnostic criteria establishes the diagnosis of Alport syndrome: Family history of haematuria, progressing mostly in males to end-stage renal disease (ESRD), Thickening and splitting of the glomerular basement membrane detected by electron microscopy, Progressive, high-frequency, sensorineural deafness, Anterior lenticonus and perimacular flecks<sup>1</sup>. These disorders are the result of mutations in type IV collagen genes. The mode of inheritance is X-linked in 80%, autosomal recessive in 15%, and autosomal dominant in about 5% of individuals with Alport syndrome<sup>1</sup>. The chief ocular findings include anterior lenticonus, cataract, central and midperipheral retinal flecks. Other ocular changes include corneal arcus, recurrent corneal erosion, posterior lenticonus, posterior polymorphous dystrophy and macular degeneration<sup>2</sup>.

### Case report

A 30 years male presented to us with diminution of vision in both eyes and mild hearing impairment. Detailed ocular examination revealed a best corrected visual acuity of 5/60 in both the eyes not improving with pin hole or glasses or by refraction. Other ocular findings present were, anterior capsular cataract in both the eyes, anterior lenticonus in both the eyes, (Fig 1) posterior lenticonus in Right eye. There was presence of Oil droplet sign in both the eyes when seen in retroillumination. Fundus evaluation revealed perimacular flecks and retinal flecks in the mid peripheral retina in both the eyes (Fig 2). Audiogram showed high frequency sensorineural type of hearing loss. Past history revealed history of renal failure and renal transplantation for which the patient

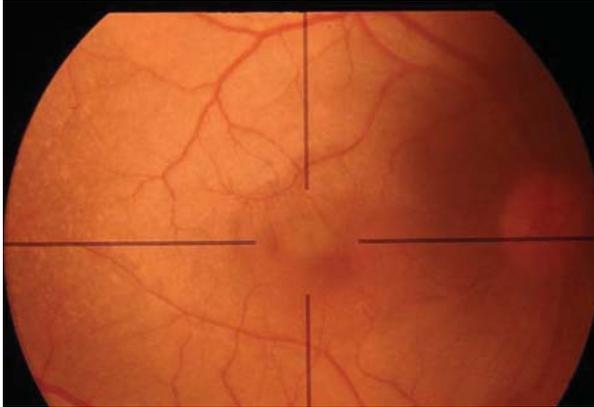
was still under medication. Patient was advised for phacoemulsification surgery with foldable intraocular posterior chamber lens implantation, in the right eye. After all the investigations, a successful cataract surgery was done in the right eye of the patient. The first post operative day's visual acuity was unaided 6/9 in the right eye improving to 6/6 with the pin hole. Patient was followed up in two weeks. In two weeks follow up patient was willing for cataract surgery in the Left eye.



**Fig 1:** Showing anterior cone shaped elevation of the crystalline lens in the right eye, along with anterior capsular cataract

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**Fig 2:** Showing retinal flecks in the right eye

### Discussion

The presence of anterior lenticonus and retinal flecks in the macula and midperipheral fundus appear to be specific for Alport's syndrome. In the case presented, white flecks were seen in both the areas of the fundus. The flecks, however, may increase and involve the periphery with advancement in age. Peripheral retinal flecks have been reported less frequently in Alport's syndrome. They tend to spare the retinal vessels. They are considered to be in the retinal pigment epithelium and angiography shows tiny hyperfluorescent window defects. The flecks in the macula and midperiphery probably have separate pathogenesis<sup>2</sup>. The other ocular findings which have been reported sporadically include recurrent corneal erosion, arcus juvenilis, punctate keratopathy, lattice dystrophy, posterior polymorphous dystrophy, cataract (capsular, polar, subcapsular, cortical, lamellar), posterior lenticonus, anisocoria, heterochromia, iris atrophy, and retinal telangiectasia<sup>2</sup>. However presence of posterior lenticonus is not so specific for Alport's syndrome, in this particular case it was present. Posterior lenticonus are more specific for Lowe's syndrome. Alport's syndrome is caused by mutation in type IV collagen genes. The genes for type IV collagen are distributed in pairs on 3 chromosomes. The genes *COL4A1* and *COL4A2* on chromosome 13 encode for the  $\alpha 1$  and  $\alpha 2$  chains, *COL4A3* and *COL4A4* on chromosome 2 encode for the  $\alpha 3$  and  $\alpha 4$  chains, and *COL4A5* and *COL4A6* on the X chromosome encode for  $\alpha 5$  and  $\alpha 6$ . The  $\alpha 1$  and  $\alpha 2$  chains are present in all basement membranes. The  $\alpha 3$  and  $\alpha 4$  chains are restricted to the basement membranes of the glomerulus, cochlea, and eye. The  $\alpha 5$  chain is expressed in the glomerulus, cochlea, eye, and epidermis. Patients with Alport syndrome have mutations in *COL4A3*, *COL4A4*, or *COL4A5*, with consequent abnormalities in the basement membranes of the glomerulus (leading to haematuria, glomerulosclerosis, and ESRD), cochlea (causing deafness), and eye (resulting in lenticonus and perimacular flecks). Children with Alport syndrome

usually have normal development and intelligence. However, a rare contiguous gene-deletion syndrome involving chromosome Xq22.3 has been described; this has been named Alport syndrome and mental retardation (ATS-MR)<sup>3</sup>. Approximately 50-80% of patients with X-linked Alport syndrome have mutations in the *COL4A5* gene. Several hundred mutations, including mis-sense mutations, splice-site mutations, and small deletions account for most cases of X-linked Alport syndrome. Few mutations have been found in more than 1 family. The most common mutation involves substitution for glycine in the collagenous domain of the  $\alpha 5$  (IV) chain by a bulky amino acid, resulting in protein-folding abnormalities. Other common mutations lead to premature termination of protein translation and loss of the carboxy-terminal NC1 domain, resulting in defective interchain association and formation of the collagen network. The X-linked Alport syndrome and the diffuse leiomyomatosis complex results from large deletion mutations in both *COL4A5* and *COL4A6*. In contrast, patients with autosomal recessive Alport syndrome have mutations in *COL4A3* and *COL4A4*. An incidental observation is that heterozygous mutations in *COL4A3* and *COL4A4* account for most cases of the relatively benign thin basement membrane disease. In some cases, mutations found in families with this disease are identical to those that cause autosomal recessive Alport syndrome in the homozygous or compound heterozygous forms. Patients with autosomal dominant Alport syndrome also have heterozygous mutations in the *COL4A3* and *COL4A4* genes<sup>1</sup>.

From Ophthalmologist's prospective, the association of 'capsular fragility' with anterior lenticonus secondary to Alport's syndrome is well documented and is supported by rare reports of spontaneous rupture of the capsule<sup>4</sup>.

In our case, however, we found that the anterior capsule was highly elastic, making the capsulorhexis technically more difficult in operated eye. The capsule elasticity was far greater than one would expect in relation to the patient's age.

John et al have also reported a case where the anterior capsules were 'tough'. It is possible that fragile capsules represent a more severe form of ocular disease<sup>4</sup>.

There are various precautions that can be taken to help complete a successful capsulorhexis in anterior lenticonus. It is worth considering a general anaesthetic in challenging cases, as the procedure may take longer and akinesia is more important. Making a small paracentesis initially allows for a complete aqueous-viscoelastic exchange in a 'sealed' anterior chamber. Use of a high molecular weight viscoelastic agent may further help deepen the anterior chamber and flatten

the anterior capsule. We found it necessary to perforate the capsule with a 26G needle and then complete the capsulorhexis using microforceps. The capsule was highly elastic and far more prone to tear out towards the lens periphery.

Having completed the capsulorhexis a gentle, but thorough, hydrodissection from several sites was made to ensure that the lens rotated well within the capsular bag. This is particularly important in younger patients when the lens can be extremely soft. Extreme caution is required when there are associated posterior subcapsular opacities or posterior lenticonus, since hydrodissection could result in a posterior capsular rupture. Under these circumstances good hydrodelineation to ensure easy nucleus rotation within the epinuclear shell is recommended. A standard 'bowl technique' was used during the phacoemulsification, the centre of the soft lens being debulked and then imploded with high vacuum during the second stage of nucleus removal. The lens cortex was aspirated in a circumferential fashion in order to avoid unnecessary tension on the zonules. The capsule was polished thoroughly to avoid capsule phimosis and possible posterior capsule opacification and a foldable, hydrophobic, acrylic IOL was inserted into the capsular bag.

Clear lens phacoemulsification is an excellent surgical procedure for the treatment of anterior lenticonus in patients with Alport's syndrome, allowing for rapid visual rehabilitation<sup>4</sup>.

### Conclusion

Alport's syndrome can be diagnosed from a careful thorough ocular examination. Patient's presenting with history of renal failure or in a state of renal failure with associated ear, nose and throat (ENT) and ocular problems should be seen with high index of suspicion to rule out Alport's syndrome. Alport's syndrome being a hereditary problem, other family members

should be examined. The role of an Ophthalmologist in managing Alport's syndrome is very important, and Ophthalmologists do play an important role in early detection of the disease or in further treatment of the disease when already diagnosed.

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