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CASE REPORT

Alport syndrome

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ABSTRACT

Objective

To present a case of Alport syndrome, its pathogenesis, etiology, clinical manifestation, diagnosis, and management.

Methods

This is a case report.

Results

A 22-year-old male presented with blurring of vision associated with bilateral anterior and posterior lenticonus. The patient had a history of blurring of vision on both eyes, occasional right lower-quadrant pain on urination, frothy urine, and bilateral hearing loss. Family medical history showed one brother who died at 15 years of heart disease, and another brother at 17 from chronic kidney disease. Slitlamp examination showed a conspicuous oil droplet reflex seen through retroillumination. Anterior and posterior bulging of the lens was noted, highly suggestive of anterior and posterior lenticonus. On indirect ophthalmoscopy, no perimacular dot-and-fleck retinopathy was seen. Further systemic workup revealed elevated serum levels of blood urea nitrogen (BUN) and creatinine, and marked proteinuria and hematuria. Ultrasound of the kidneys revealed bilateral renal parenchymal disease. Pure tone audiometry confirmed bilateral moderate sensorineural hearing loss.

Conclusions

There should be a high index of suspicion for Alport syndrome in any patient presenting with anterior and posterior lenticonus. A thorough history-taking and physical examination, including slitlamp examination through a dilated pupil, are necessary to fully support its diagnosis. There is no specifically defined treatment for Alport's syndrome; management should be individualized and approached in a multidisciplinary fashion. Lenticonus can be treated by phacoemulsification with careful capsulorrhexis.

Keywords: *Alport syndrome, anterior lenticonus, posterior lenticonus, oil-droplet reflex*

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FIRST described by Cecil A. Alport in 1927, Alport syndrome (AS) is an inherited disorder of many forms, most commonly X-linked. It typically presents with the classic triad of progressive glomerulonephritis, progressive high-tone hearing loss, and several ocular signs, the most pathognomonic of which is the presence of anterior lenticonus.[1-3]

Anterior lenticonus is a rare developmental anomaly in which there is spherical protrusion of the anterior surface of the lens into the anterior chamber, causing gradually progressive axial myopia.[1, 4-6] Most cases are associated with Alport syndrome. In contrast, posterior lenticonus, the bulging of the posterior surface of the lens into the vitreous, is not specific to AS. Anterior and posterior lenticonus in the same eye is very rare but may be present simultaneously in classical Alport syndrome.[3]

We reported a case of Alport syndrome initially presenting with gradually progressive blurring of vision in both eyes associated with bilateral anterior and posterior lenticonus. The pathogenesis, etiology, clinical manifestation, diagnosis, and management of the disorder are discussed.

CASE REPORT

A 22-year-old Filipino male, fisherman consulted at the Department of Ophthalmology and Visual Sciences, University of the Philippines–Philippine General Hospital for progressive, painless blurring of vision in both eyes for the past 10 years. There were no other associated ocular complaints.

Medical history revealed occasional right lower-quadrant pain on urination and frothy urine. There was a steady deterioration in his hearing, accompanied intermittently by low-pitched tinnitus in both ears in the past 5 years.

Family history showed that a brother died of alleged heart disease at age 15 years and another died of chronic kidney disease at age 17 years. A 51-year- old aunt was reported to have kidney problems. The genogram is shown in Figure 1.

The patient had uncorrected visual acuity of 20/70 in the right eye, best-corrected (with pinhole and with +0.50 sph and -2.00 cyl at axis 10°) to 20/40. Left eye uncorrected visual acuity was 20/100, best-corrected to 20/40 (with pinhole and with +0.75 sph and -1.25 cyl at axis 20°).

Pupils measured 2-3 mm and reacted briskly to light with no afferent pupillary defect. Direct funduscopy showed red-orange reflex with the characteristic appearance of an "oil droplet" reflex in the center of the pupils (Figure 2). This was also seen on slitlamp examination through pharmacologically dilated pupils via retroillumination. Cycloplegic refraction was performed with difficulty.

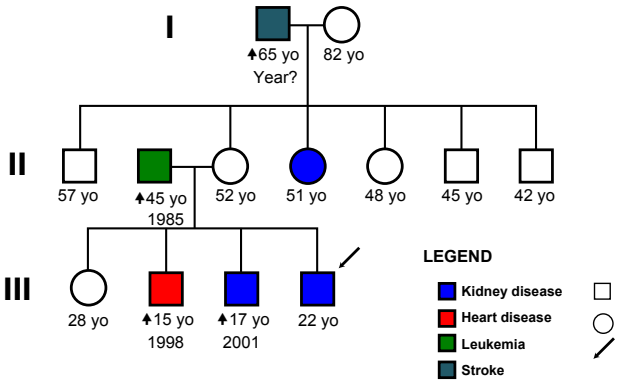

Figure 1. Family genogram

Both lenses were free of any opacity; the anterior and posterior bulging of the lenses was prominent, highly suggestive of anterior and posterior lenticonus (Figure 3). On indirect ophthalmoscopy, the posterior poles appeared normal with no perimacular dot-and-fleck retinopathy (Figure 4).

Pure-tone audiometry with speech testing confirmed bilateral moderate sensorineural hearing loss.

Complete blood count showed normal values. Serum blood urea nitrogen (BUN) and creatinine levels were elevated. Computed BUN-creatinine ratio was 5.94, indicating an intrinsic renal disease. Urinalysis showed marked hematuria and proteinuria. Chest X-ray and ECG were normal. Ultrasound of the kidney, ureters, and bladder revealed normal ureters and bladder, and an inhomogenous renal parenchymal echopattern, suggestive of bilateral renal parenchymal disease.

The patient was advised to undergo lens extraction with intraocular-lens implantation in both eyes. He was also referred to Nephrology and Otorhinolaryngology for further management of the associated medical problems.

DISCUSSION

Anterior lenticonus is a rare developmental condition in which there is a localized spherical bulging or protrusion of the anterior surface of the lens into the anterior chamber.[4-6] This increase in the anterior curvature of the lens causes a gradually progressive central or axial myopia, which may reach as high as –30 D sph.[1,5] More than 90% of cases of anterior lenticonus are said to be associated with Alport syndrome; thus, some believed that it is diagnostic of the disease.[1, 4, 6]

In contrast, posterior lenticonus is characterized by an oval or round projection of the posterior surface of the lens into the vitreous cavity.[4] It occurs in infants and young children and tends to increase in size with age. It

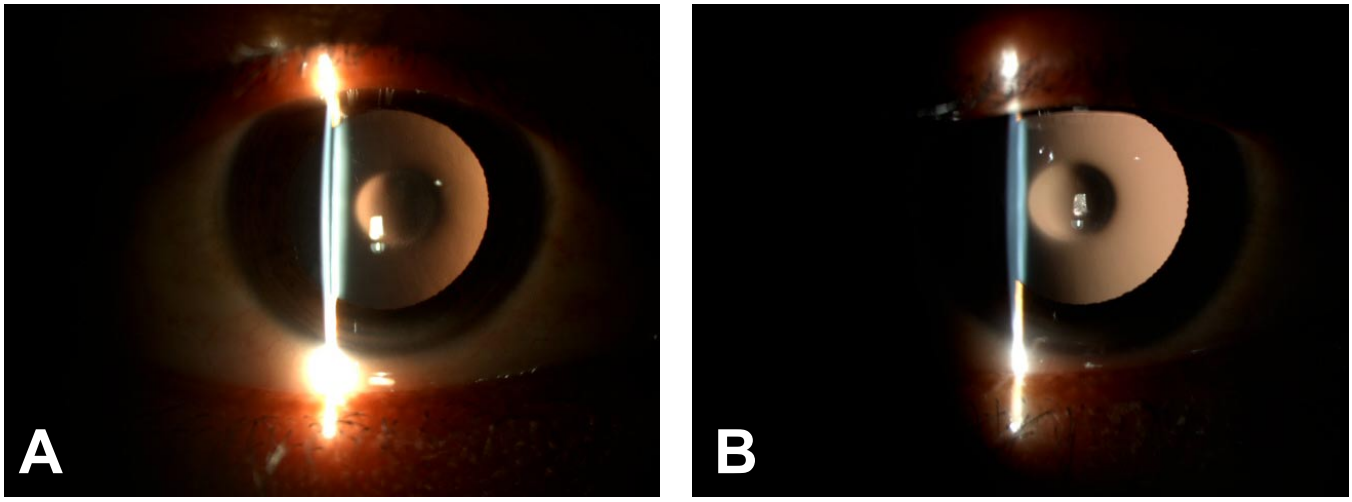

Figure 2. Oil-droplet reflex in right (A) and left (B) eyes.

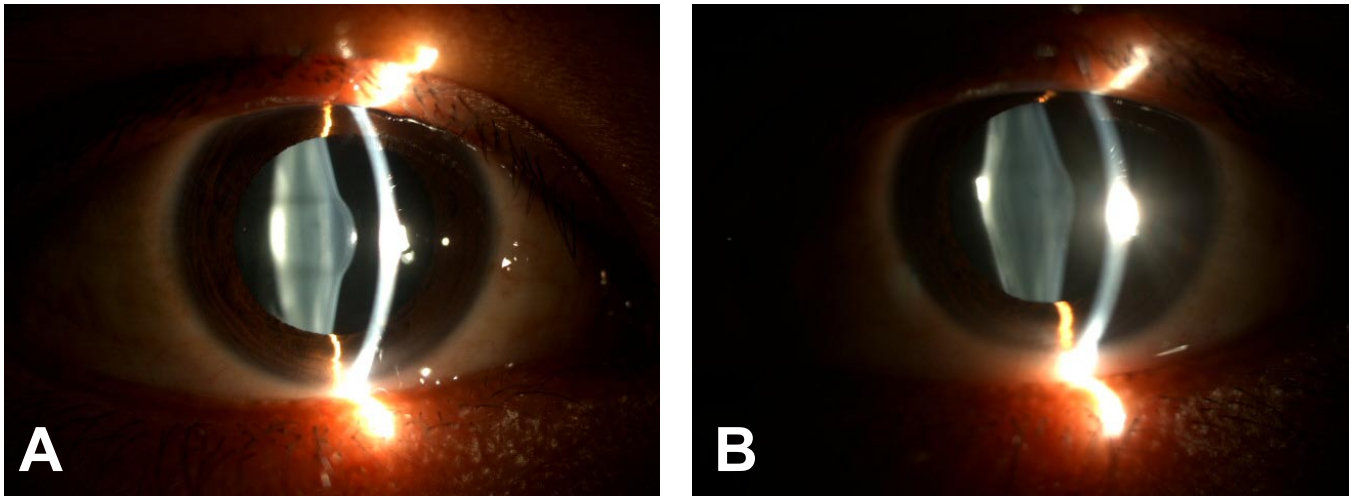

Figure 3. Anterior and posterior lenticonus in right (A) and left (B) eyes.

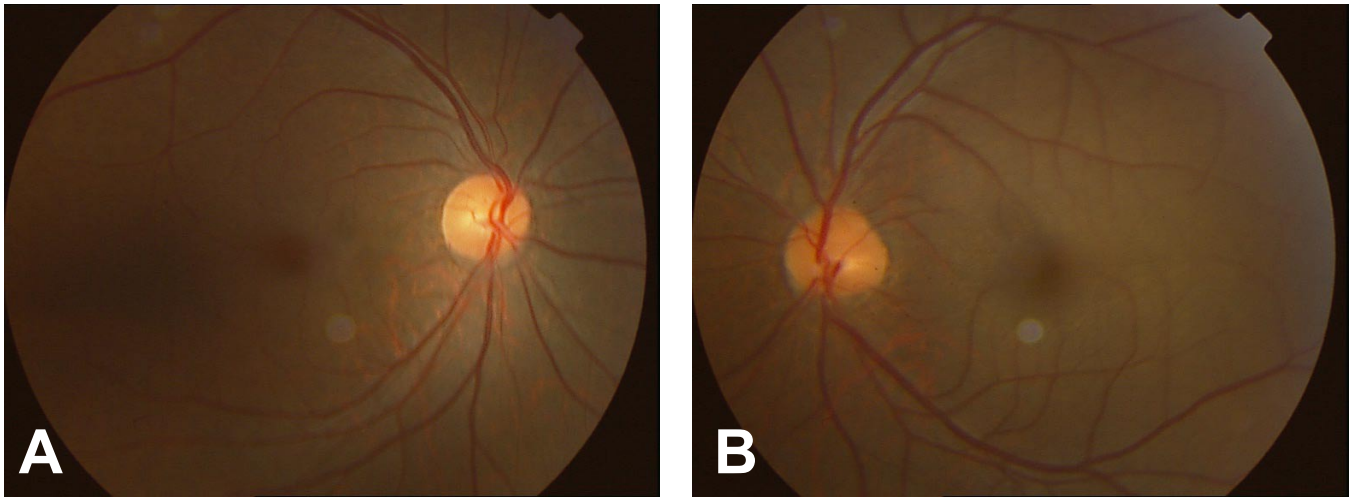

Figure 4. Fundus photos showing normal fundi in both eyes with no perimacular dot-and-fleck retinopathy.

is generally unilateral, sporadic, and not associated with systemic manifestations.[7] Although posterior lenticonus may also be found in patients with Alport syndrome, it is not specific to the disease.[1]

Alport syndrome is an inherited disorder of many forms, clinically presenting with the classic triad of progressive glomerulonephritis, progressive high-tone hearing loss, and several ocular signs, the most pathognomonic of which is the presence of anterior lenticonus.[1-3, 6, 8] Cecil A. Alport first described this disease extensively in 1927, although initial reports had previously been described several times, foremost by Guthrie in 1902. Alport studied 3 generations of a family with hereditary nephritis and deafness and noted that the most common presenting symptom was macroscopic hematuria.[1]

Alport syndrome is most commonly inherited as an X-linked disorder, accounting for approximately 80 to 85% of familial cases. The rest of these cases are inherited in either an autosomal recessive or dominant pattern, and the clinical course and manifestation may be different from the X-linked variant.[9]

The overall gene frequency of Alport syndrome is estimated at 1 in 5,000. The incidence is between1: 5,000 and 1:10,000, while the prevalence is approximately 1 in every 50,000 live births. It is said to account for about 1 to 2% of patients on renal-replacement therapy in Europe and 2.3% of the transplant population in the United States. It comprises approximately 2.7% of all patients with pediatric end-stage renal disease (1999 United States Renal Data System annual data report). These figures are probably underestimated, as the diagnosis may be missed when it occurs sporadically or in small families.[1, 10-11]

All forms of Alport syndrome are caused by mutations in the *COL4A5* collagen gene, giving rise to defective type IV collagen, which is a major structural component of basement membranes in the body, including those found in the lens, glomeruli, and cochlea.[9-11] This results in a failure of maturation of collagen in these areas, leading to diffuse thickening of glomerular basement membranes, and abnormalities of the cochlea and lenses of the eye.[10-11] Six type IV collagen genes have been cloned and characterized, and are localized in pairs on three chromosomes, namely chromosome 13, 2, and the X chromosome. Full expression of Alport syndrome requires a mutation in the *COL4A5* allele, which is carried by males with X-linked disease, or mutations in both alleles of *COL4A3* or *COL4A4* in either males or females carrying the autosomal recessive form.[12]

The most common ocular finding in Alport syndrome is anterior lenticonus. This can be explained by the fact that the lens capsule is a specialized thickened basement membrane containing collagen type IV. There is absence of a more cross-linked collagen IV network needed for development of a stronger lens. This gives rise to an inherently weak lens capsule, unable to tolerate the stress brought about by postnatal accommodation and disaccommodation of the lens. Bulging of the lens or lenticonus then occurs.[13]

As previously mentioned, X-linked AS is responsible for approximately 85% of all familial cases.[13] Males tend to be more severely affected than females.[9] It typically starts in children or young adults as asymptomatic, persistent microhematuria, which is the most common manifestation of this disease, occurring in 100% of affected individuals and in about 90% of carriers.[1, 12] Gross hematuria may occasionally occur in males together with flank pain or abdominal discomfort. Mild proteinuria and hearing loss defined as high-frequency sensorineural deafness are usually present at the time of diagnosis, as well as the deterioration in vision due to structural lens abnormalities leading to a significantly high axial myopia.[1] Sensorineural deafness occurs in approximately 80% of cases and ocular findings have been reported in roughly 40%. End-stage renal disease (ESRD) happens in 50% of affected males usually by the age of 25 and in 15% of carriers before the age of 50.[12] Hypertension is a late finding.[1]

Ocular abnormalities have been reported in 9 to 82% of patients. They are rare in childhood and increase in frequency and severity with age. The types of ocular defects described mostly involve the lens, the retina, and more rarely the cornea. The most common changes are anterior lenticonus and perimacular retinal flecks. Rarely, posterior polymorphous corneal dystrophy, which is also highly suggestive of Alport syndrome, may be seen.[1-3, 6, 8, 14] Other ocular manifestations are microcornea, other corneal dystrophies, arcus juvenalis, iris atrophy, spontaneous lens rupture, cataracts, retinal hyperpigmentation, a poor macular reflex, and hyperfluoresence on fluorescein angiogram.[2] It is important to note that anterior and posterior lenticonus in the same eye is very rare but may be present simultaneously in classical Alport syndrome, even in the absence of corneal and retinal findings.[3]

Direct ophthalmoscopy typically shows an oil-droplet reflex in the center of the pupil. As a consequence, the patient may be highly myopic centrally but emmetropic or hyperopic peripherally.[5] In the case we presented, refraction proved to be very difficult due to this phenomenon. As such, a hyperopic refraction was obtained, possibly from the peripheral pupillary area. We failed to get the patient's axial refraction, which would most likely be high myopia.

There are 4 clinical diagnostic criteria for Alport syndrome established by Flinter in 1988: (1) positive family history of macro/microscopic hematuria, chronic renal failure, or both; (2) electron microscopic evidence

of Alport syndrome on renal biopsy; (3) characteristic ophthalmic signs (anterior lenticonus or white macular flecks or both); and (4) high-tone sensorineural deafness.[1] Three out of 4 are warranted to make a diagnosis.

Positive family history. Obtaining a thorough family history is essential, especially detailed medical information on each relative. It is vital to take note of any early deaths of males in the family.[1]

Renal biopsy. There are various ultrastructural lesions of the glomerular basement membrane (GBM) seen under the electron microscope. But extensive areas of GBM thickening and splitting with inclusion of electron lucent areas with dense granulations within the lamina densa appear to be characteristic of Alport syndrome. Serial renal biopsies will show progressive deterioration.[1]

Characteristic ophthalmic signs. A thorough ophthalmologic examination through a dilated pupil is necessary to establish the diagnosis, specifically looking for the most commonly associated eye findings mentioned previously.

High-tone sensorineural deafness. A diagnosis of Alport syndrome should always be contemplated when presented with a patient with sensorineural deafness associated with hematuria, even in the absence of a positive family history or the typical ophthalmologic signs. The hearing loss is usually bilateral but is frequently subclinical at first, warranting an audiogram in any patient suspected of having Alport syndrome. The deafness is often progressive, eventually leading to the use of a hearing aid.[1]

There is no specific treatment for Alport syndrome. Patients with proteinuria may be given angiotensin-converting-enzyme inhibitors or angiotensin-II receptor antagonists, although no long-term clinical controlled trials have been done to indicate that these medicines slow the progression to ESRD. Referral to a nephrologist is essential. If renal failure advances to ESRD, dialysis and renal transplantation may be warranted.

The treatment of choice for patients with anterior lenticonus is phacoemulsification. Since there is capsular fragility, a careful capsulorrhexis with the use of a high molecular weight viscoelastic agent should be done to avoid rupture of the anterior capsule. A good hydrodissection and hydrodelineation is also important to ensure easy nucleus rotation during the procedure, but should be done with extreme caution since this could also result in posterior capsular rupture. Aspiration of the cortical material should be performed in a circumferential fashion to avoid unnecessary stress on the zonular fibers. A foldable, hydrophobic, acrylic IOL can be inserted into the capsular bag.[15]

Counseling may be beneficial to the patient and his family so they may fully understand and discuss the nature and course of the disease, as well as the possible impact that the disease may have on prognosis and costs of treatment. A genetic counselor may also be helpful if patients or their family members are considering having a child so they may be informed of the risks involved in their decision. Screening among close relatives of patients with Alport syndrome can be performed by doing routine urinalysis.

In summary, there should be a high index of suspicion for Alport syndrome in any patient who presents with anterior lenticonus, and a thorough history and physical examination is necessary to fully support its diagnosis. Careful slitlamp examination through a dilated pupil should be performed. There is no specific treatment for Alport syndrome; management should be individualized and approached in a multidisciplinary fashion, addressing the medical problems of the patients.

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