Alport’s Syndrome with Blue Sclera

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Abstract
An Indian case of Alport’s syndrome who had association of keratoglobus and blue sclerae is described.

INTRODUCTION
Alport’s syndrome has been defined as an inherited renal disease characterized by familial occurrence, in successive generations, of progressive hematuric nephritis, ultra-structural changes of Glomerular basement membrane (GBM), sensorineural hearing loss and/or ocular abnormalities. The primary defect in classical Alport’s syndrome involves the α-5 chain of type IV collagen (α-5(IV)) in the GBM and its corresponding gene COL4A5 located on chromosome Xq22.

Ocular abnormalities are seen in 30-40% cases and typically involve the lens and the retina. We hereby report an ocular abnormality previously unreported in Alport’s syndrome.

CASE REPORT
A 23 year old male presented to the medical emergency with complaints of gradually increasing facial puffiness and swelling of feet for last 10 days. There was no history of fever, sore throat, skin rash, drug intake, nausea, vomiting, headache or any cardiovascular, respiratory, or gastrointestinal complaints. The urine output was normal. He had bilateral impaired hearing since childhood for which he was using a hearing aid. Physical examination was unremarkable except that his BP was 160/110 mgHg and he had bilateral blue sclerae. There were no obvious dental, skeletal or genital abnormalities. Higher mental examination was essentially normal. Routine laboratory investigations revealed normal blood counts, blood sugar, serum electrolytes and liver function tests.

Kidney functions were deranged (blood urea 58 mg/dl, serum creatinine 2.4 mg/dl) and urine analysis was suggestive of glomerular hematuria (RBC casts, dysmorphic RBCs) with 2+ proteinuria. 24 hour urinary protein excretion was 1.5 gm, with creatinine-clearance of 55 ml/min. Chest X-ray and ultrasound of kidneys were normal.

He was further subjected to a percutaneous kidney biopsy. Light microscopy of the biopsy showed increased mesangial matrix with areas of segmental proliferation. On electron microscopy, the external aspect of the GBM was irregularly festooned and thickened, with splitting and splintering of the lamina densa, giving a typical “basket weave” appearance. Indirect immunofluorescence showed lack of fixation along the GBM. Audiometry for hearing loss revealed severe bilateral sensorineural deafness. In view of the sensorineural hearing impairment, renal involvement and the typical kidney biopsy picture, a diagnosis of Alport’s syndrome was made. A complete ophthalmological examination revealed bilateral blue sclera and a bilateral corneal bulge (keratoglobus) with a visual acuity of 6/60 and 6/36 in the right and left eye respectively. Slit lamp examination and fundus examination were both normal.

His family members were screened in view of the inherited nature of this condition. His father had died in a road side accident at the age of 62 years. He had one brother and six sisters, all of whom had blue sclera including his mother. None of the sisters or the mother had any other abnormality, while the brother showed mild bilateral sensorineural hearing loss and bilateral keratoglobus. The urine examination of sisters was normal while that of the brother showed microscopic hematuria and 1+ proteinuria.

DISCUSSION
Alport’s syndrome was first reported by Dr A Cecil Alport in 1927 in a family whose kindred had a progressive renal failure along with associated hearing loss. The incidence of gene frequency for Alport’s reported to be 1/5000 to 1/10,000 in the general population but the disease is underdiagnosed because of lack of universally accepted diagnostic criteria. It accounts for 1.1% cases of ESRD in India. The mode of inheritance is X-linked dominant in 85% of kindred while in the remaining families autosomal dominant or recessive patterns are seen. The first clinical manifestation in classical
Alport’s is a microscopic or gross hematuria in early childhood, followed by proteinuria later in the 2nd-3rd decade of life.

The hearing defect starts in early childhood and typically involves bilateral sensorineural hearing loss that can sometimes be mild, detected only by audiometric testing. Some variants of Alport’s can present as familial progressive nephritis without any hearing defect.

Ocular abnormalities include bilateral anterior lenticonus which is the most specific abnormality seen in this condition. On slit-lamp examination it gives an appearance of ‘oil-droplet in water’. Other lens abnormalities seen uncommonly are axial myopia, rupture of lens, and lens opacities. Retinal lesions are seen in 15-40% patients in the form of macular or perimacular flecks seen on fundoscopy. Other eye abnormalities like cataracts, arcus-cornealis, corneal dystrophy, pseudopappilledema, etc. are uncommonly seen. The associations of keratoglobus and blue sclerae, as seen in this patient, have never been reported earlier in Alport’s syndrome.

Other extra-renal manifestations like macrothrombocytopenia or diffuse leiomyomatosis of the esophagus may be found uncommonly in a few cases.

The differential diagnosis of Alport’s syndrome revolves around various inherited conditions with renal involvement and hearing loss as in Charcot-Marie-Tooth disease, Muckle-Wells syndrome (urticaria-deafness-amyloidosis), Branchiooto-renal syndrome, Cockayne syndrome, Refsum’s disease, Alstrom syndrome, hereditary interstitial nephritis with deafness, renal tubular acidosis with nerve deafness, and various other rare syndromes.

The clinical diagnosis can be made through a careful extended family history and a careful examination of the urinary sediment, specifically for glomerular hematuria. The extra-renal manifestations are not always found, but if present, strengthen the presumption of Alport’s syndrome and diminish the need for a biopsy. Characteristic ultrastructural changes of GBM of the kidney biopsy, with a negative immunofluorescence, and identification of type IV collagen gene mutation on linkage analysis can confirm the diagnosis. Recently the absence of staining for the alpha-5 chain of type IV collagen in the epidermal basement membrane in skin biopsy has been shown to be highly specific for X-linked Alport’s syndrome.

The disease is progressive, leading to renal failure in all affected, males usually before the age of 30 years while carrier females can have normal or mild urinary abnormalities in the form of intermittent to persistent microscopic hematuria with or without proteinuria. 5-15% of these females progress to renal failure between the ages of 60-70 years. No specific treatment is known to affect the underlying pathologic process as to alter the clinical course. Treatment of hypertension and supportive management of renal failure are indicated in patients with progressive disease. When terminal uremia occurs, dialysis and transplant are similar to those in other renal diseases, although there is a 3-5% risk of de-novo anti-GBM nephritis after transplantation.

Genetic counseling requires the correct identification of the mode of inheritance and DNA analysis may be helpful in screening cases in kindred of Alport’s cases.

References