Averting Complications in Alport's Syndrome through Early Diagnosis and Treatment

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Case Report

ABSTRACT

Alport syndrome is a rare genetic disorder of specialized basement membranes in the kidney, ear, and eye, characterized by haematuria with progressive hereditary nephritis, high-frequency sensorineural hearing loss (SNHL) and pathognomonic ocular lesions. It is one of the spectra of diseases representing hereditary nephritis, which inevitably leads to end-stage renal disease (ESRD). Microscopic or frank haematuria persistent from childhood constitutes the clinical clue for its early recognition. It occurs as a result of genetically inherited or de novo mutations in type IV collagen genes. The most common mode of inheritance is X-linked and men are more severely affected. We report a case of a middle aged man, in his fourth decade of life presenting with persistent haematuria, thrombocytopenia associated with SNHL and anterior lenticonus, diagnosed as a previously undetected case of Alport syndrome.

KEY WORDS: alport's, end-stage renal disease (ESRD), sensorineural hearing loss, syndrome

INTRODUCTION:

Alport syndrome (AS) is a genetic disease wherein the collagen mutation affects kidneys, ears, and eyes. The syndrome was described by Dr Alport in year 1927, as observed in a british family, in which many members developed renal disease as well as deafness. He noted that affected men in the family died as a result of their kidney problems, whereas females were less affected and lived until old age[1].

Alport syndrome is a familial renal disorder caused by pathogenic variants in COL4A3, COL4A4, and COL4A5 that result in abnormalities of the collagen IV α345 network of basement membranes. Alport syndrome can be transmitted in an X-linked (XLAS), autosomal dominant (ADAS), or autosomal recessive (ARAS) pattern[2]. The spectrum of renal involvement ranges from isolated, non-progressive haematuria to progressive nephropathy characterized by haematuria, proteinuria, and chronic kidney disease (CKD) and end-stage renal disease (ESRD). Affected individuals often have sensorineural hearing loss and characteristic ocular abnormalities. Rare individuals have associated aortic disease or diffuse leiomyomatosis. Platelet disorders and leiomyomatosis, usually involving hollow organs like the trachea, esophagus and the female genital tract, have also been described.

The incidence of Alport's syndrome is about 1 in 5000 in the general population[3]. Normally, the glomerular basement membrane (GBM) contains the tissue specific X3, X4, X5 chains of type IV collagen. However, in Alport's syndrome, this network is disrupted and replaced by X1 and X2 chains. As a result, the GBM which appears structurally normal in early life becomes thin with time. It may later progress to thickening of the GBM which later undergoes the process of splitting and then degeneration[4].

CASE REPORT:

A 40 year old male came as out-patient in the Department of Medicine with chief complaints of gradually progressive hearing loss for last 10 years, diminution of vision for last 3 - 4 years, and reddish discoloration of urine for last 2 - 3 years. He also complained of decreased urine output since two months. Family history was negative for similar complaints, and the patient does not recall anything significant. The patient was admitted for investigations. On admission his general condition was fair, pulse was 80/min regular, BP 110/60 mm of

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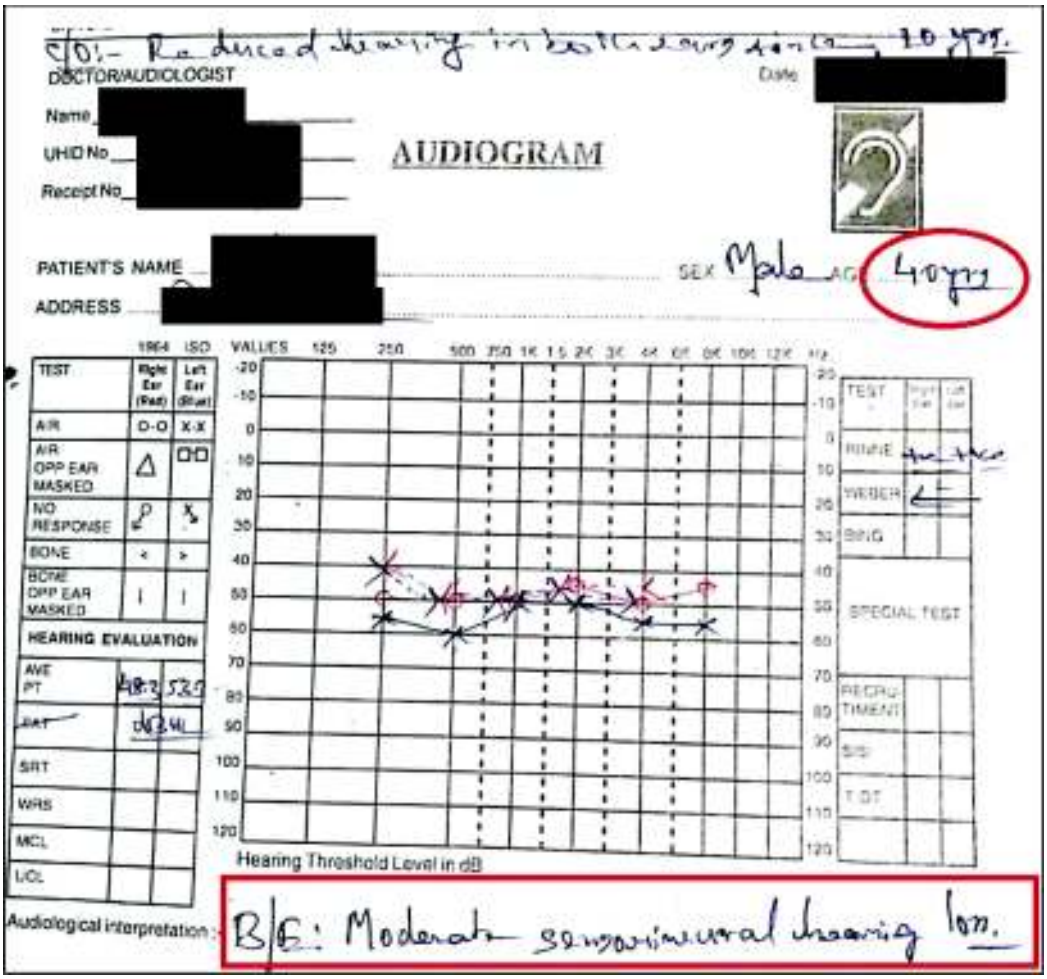

Figure 1: PTA of the patient showing B/L sensorineural hearing loss.

Hg in right arm supine position. General and systemic examinations were normal. Total WBC Count was 6300. Haemoglobin was 15.1 g/dl. Thrombocytopenia was noted on two occasions with value of 118,000 and 85,000 respectively (range 150,000-400,000). Urine routine microscopy showed 25-30 Red Blood Corpuscles with albumin in traces and 4 to 5 pus cells. No cast, epithelial cells or bacteria were present. Blood urea and creatinine were 24 mg/dl and 0.89 mg/dl respectively.

The patient was referred to the Department of Otolaryngology for assessment of hearing loss. Pure Tone Audiometry (PTA) was advised which showed bilateral moderate Sensorineural Hearing Loss (Figure 1). Referral to Ophthalmology was made and it informed severe refractory error (vision of 2/60 and refractory error of -19.75/-3.0 in right eye; vision of 1/60 and refractory error of -19.50/-5.0 in left eye. The best corrected visual acuity was 6/36 in both eyes for distant and N/24 for near vision. Slit lamp examination revealed cone shaped lens protruding outwards i.e. Anterior Lenticonus (Figure 2) In both eyes.

DISCUSSION:

With incidence of 1 in 50,000 live births, the Alport syndrome accounts for 0.3 to 2.3% of end-stage kidney disease. Mode of inheritance is X-linked in 80%, autosomal recessive in 15%, and autosomal dominant in 5%[5]. It is caused by mutations in the COL4A5 collagen gene, giving rise to defective type IV collagen, which is a major structural component of the basement membranes in the renal glomeruli, cochlea, and lens. Sensorineural deafness occurs in

Figure 2: Slit lamp examination showing anterior lenticonus.

approximately 80% of the cases and ocular findings have been reported in roughly 40%.

The diagnostic criteria for the Alport syndrome include: (a) family history of nephritis with unexplained haematuria; (b) persistent haematuria without evidence of other renal problems; (c) bilateral sensorineural hearing loss up to 2000 - 8000 Hz; (d) mutation in the COL4A5 gene; (e) immunohisto-chemical evidence of complete lack of the Alport epitope in the glomerular basement membrane (GBM); (f) GBM thinning or splitting; (g) ocular lesions like anterior lenticonus, posterior subcapsular cataract, posterior polymorphous corneal dystrophy, and retinal flecks; (h) progression to end-stage renal disease (ESRD) in at least two family members; (i) macrothrombocytopenia; and, (j) diffuse leiomyomatosis of the esophagus or female genitalia. Out of these ten findings, at least four of these must be present for diagnosis of the Alport syndrome[6].

It is important to diagnose the Alport syndrome in the early stage of the disease and it should be effectively managed by a combined approach by nephrologists, the otorhinolaryngologists, and the ophthalmologists. The above case had four distinct features to identify it as Alport`s Syndrome. These were (a) persistent haematuria without evidence of other renal problems; (b) bilateral sensorineural hearing loss up to 2000 - 8000 Hz; (c) anterior lenticonus and (d) macrothrombocytopenia.

CONCLUSION:

There is no definite treatment for the Alport syndrome. Early ophthalmological intervention should be carried out for better visual prognosis.[7] Angiotensin-Converting-Enzyme (ACE) inhibitors have been used to treat hypertension and reduce proteinuria. Cyclosporine has also been used to halt disease progression in those patients with severe proteinuria. In patients with ESRD, both dialysis and renal transplantation are done. Gene therapy for the Alport syndrome is being studied. Animal studies are underway, to evaluate delivery of the human alpha-5 (IV) chain of GBM in a canine model of the X-linked Alport syndrome.

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