RENAL FAILURE IN THE YOUNG BOY WITH ALPORT'S SYNDROME

Umair Ahmed Siddiqui, Abdul Halim

Military Hospital, Rawalpindi

INTRODUCTION

Cecil Alport, in 1927, described a hereditary glomerulopathy. The original family [1] that he described had dominantly inherited kidney disease that was characterized in both sexes by hematuria and urinary erythrocyte casts, variable proteinuria, and by hearing loss and renal failure in males. Affected males died in adolescence of uremia or end-stage renal disease. Since then other individuals (phenotypes) have been recognized with ocular defects and well preserved hearing, though hearing loss is the most common extra-renal manifestation [2]. Other phenotypes including leiomyomatosis and facial malformation with mental retardation and elliptocytosis have been recognized. Still other forms are associated with megathrombocytopenia and granulocyte defects.

Alport's syndrome (AS) is a progressive non-immune glomerulonephritis with a prevalence of about 1 in 50,000 live births contributing nearly 2% new cases of end-stage renal disease {3-5}. It is a genetically heterogeneous disease with X-linked (80%), autosomal recessive (15%), and autosomal dominant (5%) variants arising from a number of mutations in genes encoding for several members of type IV collagen [6]. X-linked Alport arises from mutation in COL4A5 gene; autosomal recessive from mutations in COL4A3 or COL4A4 genes 6. These mutations impair the deposition of an alpha [3-5] type IV collagen chain in the glomerular basement membrane (GBM), leading to glomerulosclerosis.

The changes on light microscopy are nonspecific and may include focal glomerular hypercellularity, glomerulosclerosis and a mild lymphocytic interstitial infiltrate consisting of lipid laden foam cells. The electron microscopy may be diagnostic if GBM splitting in a basket weave pattern is seen. This change increases in severity and proportion with age [7]. Asymptomatic microhematuria and recurrent gross hematuria occurs especially in childhood. Its absence in males by age 10 years rules out the disease [3]. Progressive renal insufficiency, hypertension, and proteinuria occur over time. End-stage renal disease (ESRD) usually occurs in males between the ages of 16-35 years 7. The diagnosis is suspected from the family history of renal failure and deafness, and differentiated from IgA nephropathy and thin basement membrane disease. In 15% cases, however, no family history is forthcoming and diagnosis is made on renal histology [8]. No curative treatment is available and either dialysis or transplantation can be performed in those developing ESRD. Patients with AS, lack the Goodpasture antigen. A normal allograft is exposed to antibodies against the α5 or the α3 chains but only a minority develops severe glomerulonephritis or Good-Pasture disease leading to graft loss.

CASE REPORTS

Case No. 1

A 13-year-old boy, presented at CMH Pano Aqil with a one month history of decreased urine output, vomiting, breathlessness and epistaxis. Later he was shifted to MH Rawalpindi because of uremia and altered consciousness. His birth and developmental history was normal. He is the youngest of three brothers who are healthy with no microhematuria. Father and mother are not first-degree relatives. Mother was not available for urinalysis. There is no history of gross hematuria in the past or renal disease and kidney failure among family members.

Examination at MH Rawalpindi showed an emaciated boy who was drowsy,

Correspondence: Brig Abdul Halim, Advisor of Nephrology, Prof of medicine, MH Rawalpindi
Email: ambreen69@hotmail.com
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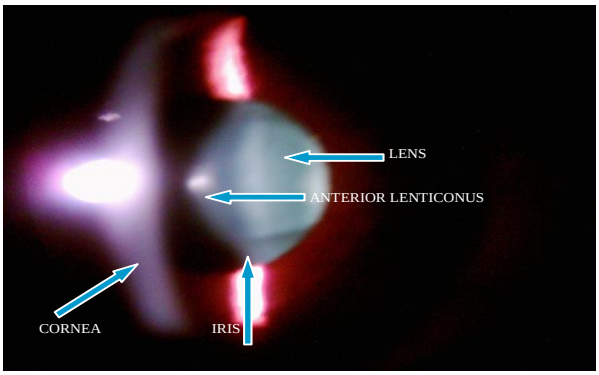

Fig.1: Anterior Lenticonus

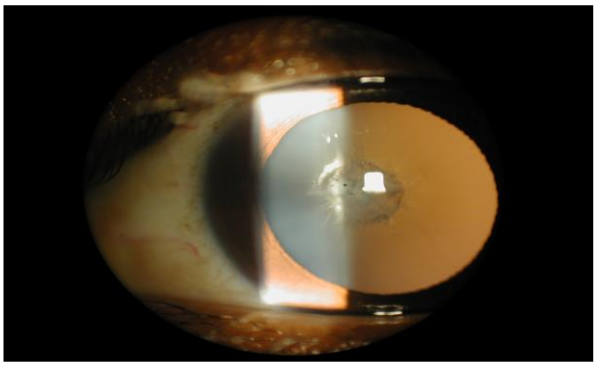

Fig.2 Anterior Subcapsular Cataract

Fig.4: Electron-micrograph, showing irregular thick and this regions basement membrane

breathless, markedly pale, and hypertensive (140/90 mm Hg). There were bibasilar crackles in the chest. Abdomen did not reveal any masses. Blood urea was 52.6 mmol/l, creatinine 1698 umol/l and hemoglobin 7 g/dl. Proteinuria (2+) microscopic hematuria (RBC 8-10/HPF), with few granular casts on urinalysis. Kidneys were small for his age with grade II renal parenchymal disease on ultrasound. Hemodialysis was started. Further testing for acute glomerulonephritis (ANA, ANCA, Anti-GBM, HbsAg, Anti-HCV) were negative. Serum complements were normal. Radionucleide imaging suggested poor functioning kidneys. Considering hereditary nephritis as a possibility further tests were ordered. Slit-lamp eye exam found a right anterior lenticonus (fig. 1), left anterior subcapsular cataract (fig. 2) and pigmentary flecks in the fundi. On pure-tone audiometry, a mild sensorineural hearing loss was present bilaterally (fig-3). These findings were consistent with Alport's Syndrome. He is on chronic hemodialysis (twice weekly) and his father has been counseled regarding early kidney transplant.

Case No. 2

A sixteen-year-old boy had markedly raised blood urea and creatinine, and nearing-end-stage renal disease. He was found to have microscopic hematuria at the age of two years, concurrent with upper respiratory tract infection. He has not had any evidence of gross hematuria and the extent of microscopic hematuria has been variable. His past medical history seems to be unremarkable and his family history is not suggestive of kidney failure in any close relatives. He is one of three siblings. His younger sister had also been noted to have microscopic hematuria. Siblings are otherwise healthy. There was no history of deafness in his family. A tall young man, having a blood pressure of 150/95 mm Hg; his ENT and Eye examinations were within normal limits. Chest was clinically clear. Abdomen was soft and without any masses. Urinalysis showed a light cola colored urine, 4+ proteins, and numerous RBCs (glomerular origin). Few granular and mixed RBC casts were present as well. Blood urea was 21 mmol/l, creatinine was 558 umol/l, normal electrolytes, total protein 53 g/l, albumin 31 g/l, normal complements and blood glucose. A renal biopsy performed in 1996 revealed an essentially normal light microscopy (except for a small focus of interstitial lymphocytic infiltrate) and indirect immunofluorescence. However, on electron microscopy (fig. 4), the peripheral basement membrane (BM) showed irregular thick and thin regions. The thick BM showed a basket-weave pattern of splitting, associated with punctate electron dense dots (not immune deposits). The findings were consistent with a hereditary nephropathy, and, with clinicopathologic correlation, consistent with

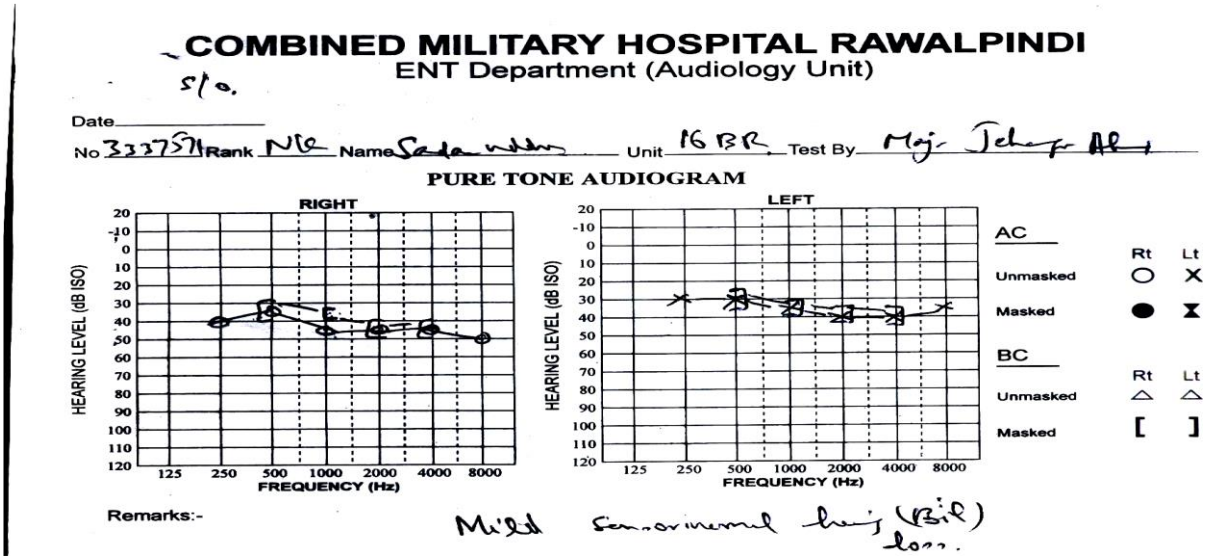

Fig. 3 Pure Tone Audiogram showing bilateral mild sensorineural hearing loss

Alport's syndrome. He has since undergone renal transplantation, with a well functioning allograft.

DISCUSSION

The initial renal manifestation of Alport's syndrome (AS) is microhematuria and is present from early in life in males [9]. The diagnosis of AS is usually suspected from a family history of renal failure and deafness [8] The first case somehow only came to light because of severe uremia, in the absence of a past history of hematuria or family history of renal failure but in the second case history of microhematuria in childhood along with presence of asymptomatic microhematuria in a sibling suggested AS. Interestingly enough both the cases lacked clear evidence of deafness in the close family members. In upto 15% of cases of AS a family history is lacking and represents autosomal recessive disease or newer COL4A5 mutations [10]. A histological diagnosis was only made in the second patient as hearing loss, ocular features and family history was not forthcoming. In the first case, however, the presence of high frequency hearing loss along with lenticonus clinched the diagnosis, as anterior lenticonus, present in 20 to 30% of X-linked inheritance, is pathognomonic of AS [3]. A detailed clinical and laboratory analysis of the two kindred including detection of mutations by polymerase chain reaction or DNA sequencing was not done, being not available. A high index of suspicion in children and adolescents presenting with gross hematuria without an obvious surgical cause, or found to have microhematuria incidentally, should lead to a detailed family history, and further testing and evaluation for AS. In the second case, no evidence of anti-GBM glomerulonephritis is present after one year of renal transplant, the incidence of which is probably <10%. Most patients with AS who do not develop this complication do well after transplantation [11].

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