Case Report

ALPORT SYNDROME IN A 32-YEAR-OLD: A CASE REPORT.

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Abstract

Background: Alport syndrome refers to a group of inherited, heterogeneous disorders involving the basement membrane of the kidney and frequently affecting the cochlea and eyes as well. These disorders are the result of mutations in type IV collagen genes. It is a rare disease accounting for approximately 3% of children and 0.2% of adult with end stage renal disease.

Case presentation: He presented with one-year history of inability to hear well with both ears and blurring of vision, and six-month history of recurrent episodes of haematuria. Following the report of renal biopsy, a diagnosis of chronic kidney disease secondary to Alport syndrome was made. He was counselled on the nature of his illness and was commenced on tablet loop diuretics (frusemide 40 mg daily) to improve diuresis and relieve oedema. For blood pressure control and proteinuria, he was placed on tablet amlodipine 10 mg and valsartan 320 mg. He was also placed on haematinics. Dyslipidaemia was treated using atorvastatin 10 mg daily. He was reviewed by the ENT surgeon and ophthalmologist, and presently being followed up in the renal unit.

Conclusion: Renal prognosis in Alport syndrome depends on the kind of mutation causing the condition. Early diagnosis and prompt and early management will help improve prognosis and the patient's quality of life.

Keywords: Alport syndrome, Heterogeneous disorders, Mutations, End stage renal disease.

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INTRODUCTION

Alport syndrome refers to a group of inherited, heterogeneous disorders involving the basement membrane of the kidney and frequently affecting the cochlea and eyes as well. These disorders are the result of mutations in type IV collagen genes.

Alport syndrome is a rare disease accounting for approximately 3% of children and 0.2% of adult with end stage renal disease in United State of America.[1] In Europe, Alport syndrome accounts for 0.6% of patients with end stage renal disease. There is still paucity of information on prevalence of Alport syndrome in Nigeria.

CASE PRESENTATION

He was apparently well until a year prior to presentation when he developed inability to hear well with both ears. This was insidious in onset, initially affecting only the left ear but subsequently involved the right with no associated ear discharge. There was no history of trauma to the ears or trapping of foreign object in the ear and there was no history of use of any toxic medication.

Within that same period, he started noticing blurring of vision in both eyes. There was no associated redness, pain or itching of the eyes but there was positive history of occasional tearing of the both eyes.

Six months prior to presentation, he developed recurrent episodes of haematuria. This occurs at least two times in a month for which he usually visited a peripheral hospital where he was often been treated for urinary tract infection. Following the last episode of haematuria which occurred 2 days prior to presentation, he was referred to our centre for expert treatment.

There was positive history of frothiness of urine and oliguria. He had positive history of leg swelling and occasional facial puffiness but no abdominal swelling. There was no previous history of sore throat or skin rashes. He had a similar episode of haematuria at the age of 9 years and has not reoccurred since then until the present episodes.

There was no history of indiscriminate use of NSAIDs or herbal concoction. He is not a known hypertensive or diabetic. He has visited several eye and ear clinics within the period of the illness but there was no obvious improvement. He is not allergic to any drug.

He is the fifth child in a family of five, his mother was alive and but his father died five years previously from ESRD. His eldest brother is currently undergoing haemodialysis for ESRD at the age of 48 years. He neither takes alcoholic beverages nor tobacco in any form.

The general physical examination revealed a young man who was afebrile, pale, anicteric, not cyanosed and not dehydrated. There was no peripheral lymphadenopathy or finger clubbing. He had mild bilateral ankle oedema. The weight was 72kg.

Pulse rate was 86 beats/minute, full volume and regular. There was radio-radial synchrony but no radio-femoral delay. He had no thickened arterial wall or locomotor brachialis. The blood pressure was 140/100mmHg.The jugular venous pressure was not raised. The apex beat was localized at 5th left intercostal space mid-clavicular line and not heaving. The heart sounds were 1st and 2nd but there was no murmur.

The respiratory rate was 16cycles per minute and the tracheal was central. There was equal chest movement. There was no other significant finding elicited.

The abdomen was uniformly full and moves with respiration. The liver and spleen were not palpably enlarged and the kidneys were not ballotable. He had no ascites.

He was conscious and alert, well oriented in time person and place. No signs of meningeal irritation. The tone, power and reflexes were normal globally.

A clinical impression of CKD secondary to chronic glomerulonephritis was made. Dip stick urinalysis showed proteinuria of 3+ (500mg/dl), blood (+++), urine of low specific gravity of 1.010 and acidic with PH of 5. Others were normal.

Urine microscopy revealed red blood cells of 2 – 4 per high power □eld(hpf), epithelial cells of 0 – 1per hpf. There were no cast or crystals. Urine protein creatinine ratio (uPCR) was 300mg/mmol. Results of haematology and biochemical tests are stated in table 1. Serology screening for hepatitis B, hepatitis C and HIV were negative. Renal ultrasound scan showed left kidney of 10.2cm x 4.6cm and right kidney of 10.4cm x 4.5cm with increased echogenicity and loss of corticomedullary differentiation.

Fundoscopy done revealed a dot and fleck retinopathy of both eyes. Audiometry done showed evidence of sensorineural deafness [figure 1]. Successful renal biopsy was done and the tissue was examined under light microscopy [figure 2]. This showed segmental increase in the mesangial matrix without associated increase in mesangial cellularity (in keeping with glomerulosclerosis). This is shown in figure 2. Genetic testing was not done due to lack of facility in my centre.

Table 1: Haematological and biochemical results at presentation

Investigations	Results	Reference range
Haematology		
Haemoglobin (g/dl)	9.6	12-16
White blood cell (L-1)	4.5 x 109	4-11 x 109
Platelet (L-1)	160 x 109	140-400 x 109
Neutrophil (%)	70	40-75
Lymphocyte (%)	28	20-45
Eosinophil (%)	2	1-6
ESR (MM/HR)	10	5-7
Biochemistry		
Serum Urea (mmol/l)	12.4	2.4-6.0
Serum creatinine	230	60-120
(mmol/l)	130	135-145
Sodium (mmol/l)	4.35	3.5-5.0
Potassium (mmol/l)	20	24-30
Bicarbonate (mmol/l)	2.2	2.2-2.6
Serum calcium (mmol/l)	1.6	1.1-1.7
Phosphate (mmol/l)	250	120-420
Uric acid (mmol/l)	68	62-80
Total protein (g/l)	24	36-50
Serum albumin (g/l)	5.60	<5.2
Total cholesterol (mmol/l)	2.0	0.3-1.7
Triglyceride (mmol/l)	1.0	>1.12
HDL (mmol/l)	3.69	<2.6
LDL (mmol/l)	4.8	3.3-5.5
FBG (mmol/L)		

eGFR was 35ml/min/1.73m^2(MDRD)

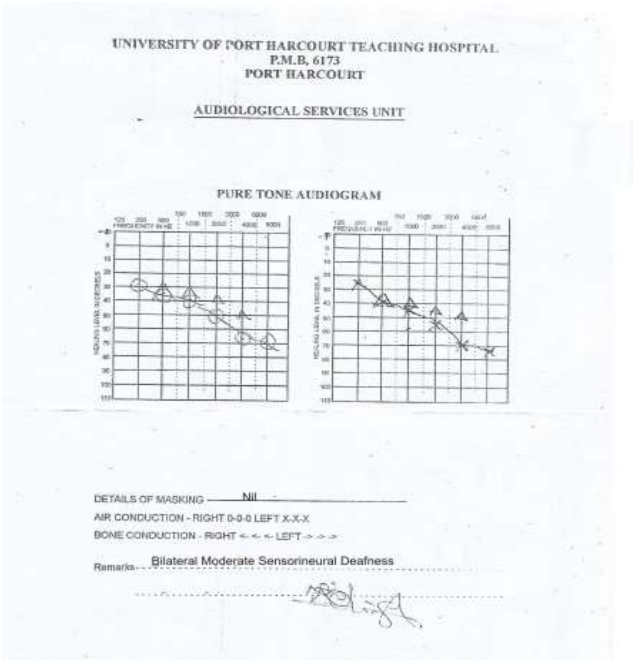

Figure 1: Audiometry result showing Sensorineural deafness.

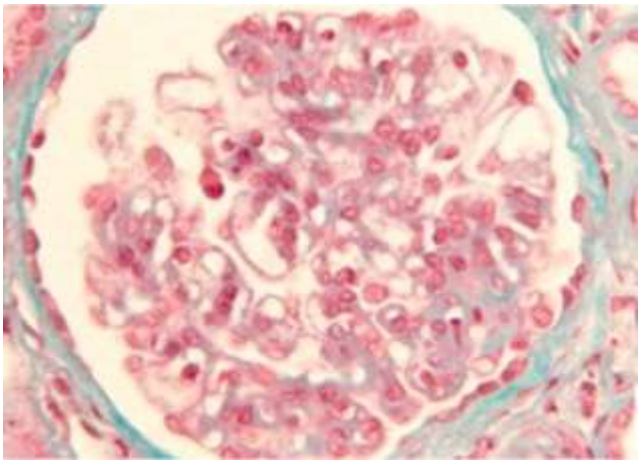

Figure 2: Light microscopy histology of the kidney showing increase in mesangial matrix (glomerulosclerosis) (Masson-Trichrome x 630).

A diagnosis of chronic kidney disease secondary to Alport syndrome was made. He was counselled on the nature of his illness and was commenced on tablet loop diuretics (frusemide 40 mg daily) to improve diuresis and relieve oedema. For blood pressure control and proteinuria, he was placed on tablet amlodipine 10 mg and valsartan 320mg. He was also placed on haematinics. Dyslipidaemia was treated using atorvastatin 10mg daily. Iron deficit was calculated and corrected using intravenous iron sucrose and he was subsequently commenced on erythropoietin (Recormon 4,000 IU weekly). He was placed on dietary low salt (<5.0g/day) and low protein (0.8g/kg/day) of high biological value.

He was reviewed by the ENT surgeon who subsequently offered him a hearing aid following the audiometry result that showed sensorineural deafness. He was also reviewed by the ophthalmologists who advised conservative management.

He is presently being followed up in the renal unit. His clinical condition has improved, haematuria has subsided, and the renal function on the last visit showed creatinine of 200umol/l, urea of 10mmol/l, and urinalysis showed proteinuria of 30mg/dl.

DISCUSSION

In 1927, Alport first described the combination of progressive hereditary nephritis with sensorineural

deafness. The presence of persistent glomerular haematuria, family history of Alport syndrome or renal failure of no other obvious cause, progressive high frequency sensorineural deafness, anterior lenticonus and perimacular flecks, and lack of alpha 3,4,5 collagen IV chains in glomerular basement membrane suggests the diagnosis of Alport syndrome.[2] The index patient presented with recurrent haematuria, difficulty in hearing with both ears, father died from complications of ESRD, the elder brother is currently on chronic haemodialysis for ESRD and fundoscopy done at presentation revealed dot and fleck retinopathy.

The diagnosis of Alport syndrome can be confirmed by the presence of splitting or lamellation of glomerular basement membrane on electron microscopy or a pathogenetic mutation in the COL4A5 gene or 2 pathogenic mutations in COL4A3 or COL4A4 genes.[3] Though we were unable to do electron microscopy or genetic testing in this patient due to lack of facility but clinical presentations and light microscopy histology findings showed some consistency with Alport syndrome.

Children with Alport syndrome initially present with only persistent haematuria and a family history of haematuria. Auditory or ocular manifestation may appear later in life. Our patient first developed haematuria at the age of 9 years but the hearing impairment and visual defect began to manifest at the age of 32. The typical changes of the glomerular basement membrane are also age dependent and may be absent from initial biopsy samples obtained from young children with Alport syndrome.

Alport syndrome, which is genetical heterogeneous, is caused by defects in the genes encoding alpha-3, alpha-4 and alpha-5 chain of type IV collagen of the basement membranes. The estimated gene frequency ratio of Alport syndrome is 1:5000. Three genetic forms of Alport syndrome exists and these are: XLAS which results from mutations in the COL4A5 gene, accounts for 85% of case of Alport syndrome. Autosomal recessive Alport syndrome (ARAS) caused by mutations in either the COL4A3 or COL4A4 gene, responsible for approximately 10-15% of cases. Autosomal dominant Alport syndrome (ADAS) is rare and caused by mutations in either the COL4A3 or COL4A4 gene in at least some families and accounts for the remainder of cases.

More than 300 mutations have been reported in the COL4A5 genes from families with XLAS. Most COL4A5 mutations are small, these include missense mutations, splice-site mutations and deletions of less than 10 base pairs.

Approximately 20% of mutations are major rearrangements at the COL4A5 locus. A particular type of deletion spanning the 5'ends of the COL4A5 and COL4A6 genes is associated with rare combination of XLAS and diffused leiomyomatosis of the oesophagus, tracheobronchial tree and female genital tract.

In patients with Alport syndrome, no mutations have been identified solely in the COL4A6 gene. To date, only 6 mutations in the COL4A3 gene and 12 mutations in the COL4A4 gene have been identified in patients with ARAS. Patients are either homozygous or compound heterozygous for their mutations and their parents are asymptomatic carriers. The mutations include amino acid substitutions, frameshift deletions, missense mutations, in-frame deletion and splicing mutations. ADAS is rarer than XLAS or ARAS. Recently, a splice site mutation resulting in skipping of exon 21 in the COL4A3 genes was found in ADAS.[4]

Gross haematuria or microscopic haematuria is the most common and earliest manifestation of Alport syndrome. Microscopic haematuria is observed in all males and in 95% of females. This condition is usually persistent in males, whereas it can be intermittent in females. Haematuria is usually discovered during the first year of life in males. If male patient does not present with haematuria during the first decade of life, he is unlikely to have Alport syndrome. Our patient had haematuria at the age of 9 years.

Proteinuria is usually absent in childhood but eventually develops in male with X-linked Alport syndrome (XLAS) and in males and females with ARAS. Proteinuria usually progresses with age and can occur in the nephrotic range in as many as 30% of patients. Our patient had nephrotic range proteinuria at presentation. Significant proteinuria is infrequent in females with XLAS but it may occur. Hypertension is usually present in males with XLAS and in males and females with ARAS. Incidence and severity increase with age and degree of renal failure. My patient had moderate hypertension as at when he presented to us.

Sensorineural deafness is a characteristic feature observed frequently, but not universally in patients with Alport syndrome. This patient presented with hearing impairment and audiometry carried out on him confirmed sensorineural deafness. Hearing loss is never present at birth, bilateral high frequency sensorineural hearing loss usually begins by late childhood or early adolescence, generally before the onset of renal failure. Features of renal failure began to manifest in our patient by the age of 32 years and this started one year after the onset of hearing impairment. About 50% of male patients with X-linked Alport syndrome show sensorineural deafness by age 25 years and about 90% are deaf by the age of 40 years.

Anterior lenticonus, which occurs in approximately 25% of patients with XLAS is the pathognomonic feature of Alport syndrome. In this condition, the lens surface protrudes conically into the anterior chamber of the eye because of a thin and fragile basement membrane of lens capsule. The lenticonus is most marked anteriorly because the capsule is thinnest there, the stresses of accommodation are more marked and the lens is least supported. Anterior lenticonus is not present in birth but is manifested by a slowly progressive deterioration of vision, requiring patients to change the prescription of their glasses frequently.

Dot and fleck retinopathy is the most common ocular manifestation of patients with Alport syndrome occuring in approximately 85% of males with XLAS. Rarely observed in childhood, it usually becomes apparent at the onset of renal failure. Our patient had fundoscopy done at presentation which showed dot and fleck retinopathy. Dot and fleck retinopathy is usually asymptomatic, with no associated visual impairment or night blindness, though my patient had an associated blurring of vision and occasional tearing.[5]

There is no definite treatment for Alport syndrome. Research indicates that angiotensin converting enzyme inhibitor (ACEi) can reduce proteinuria and the progression of renal disease. Thus, the use of ACEi is reasonable in patients with Alport syndrome who have proteinuria with or without hypertension. Some reports suggest that cyclosporine may reduce proteinuria and stabilize renal function in patients with Alport syndrome; however, the studies were small and uncontrolled. Moreover, reports suggest that patient response to cyclosporine can vary and that the drug may accelerate the development of interstitial fibrosis due to calcineurin-induced nephrotoxicity.[6]

As renal failure advances, appropriate replacement therapy should commence. Therapy includes erythropoietin for chronic anaemia, phosphate binders and vitamin D to manage osteodystrophy and antihypertensive therapy to control hypertension. Patient with end stage renal disease should have renal replacement therapy. Recurrent disease does not occur in the transplanted kidney, and the allograft survival rate in these patients is similar to that in patients with other renal diseases. However, anti GBM nephritis develops in a small percentage of transplant patients with Alport syndrome.

Renal prognosis in Alport syndrome depends on the kind of mutation causing the condition. The probability of ESRD in people younger than 30 years is significantly high (90%) in patients with a large rearrangement of the COL4A5 gene than it is in those with minor mutations. End stage renal disease develops in virtually all males with XLAS, with degree of proteinuria in the patients being predictive of the rate of the disease. Female

patients with XLAS tend to have mild renal disease with many surviving to old age.[7] Renal prognosis for all patients, male and female, with ARAS is poor, with most progressing to ESRD.

CONCLUSION

Renal prognosis in Alport syndrome depends on the kind of mutation causing the condition. Early diagnosis and prompt and early management will help improve prognosis and the patient's quality of life.

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