University Journal of Medicine and Medical Specialities

ISSN 2455- 2852 2018, Vol. 4(1)

TWO CASES OF ALPORT SYNDROME

UPAMA
Department of General Medicine,
MADURAI MEDICAL COLLEGE AND HOSPITAL

Abstract : Alport syndrome is an inherited condition due to mutations in genes coding for alpha chains of type IV collagen. Here we present two cases, a 19 years old female and a 14 years old male with family history of consanguinity and end stage renal disease admitted with complaints of hematuria and facial puffiness respectively. On further evaluation they were found to have elevated renal parameters, anterior lenticonus and sensorineural hearing loss and were diagnosed as Alport syndrome.

Keyword : Alport Syndrome, lenticonus, sensorineural hearing loss

Case series : Case1 19 years old female born to parents of third degree consanguinous marriage admitted with complaints of hematuria for 2 weeks. She had history of hearing impairment since 10 years of age and visual impairment for past 3 years. Her elder brother who also had hearing impairment died of renal failure at the age of 25 years. On examination her vitals were stable and system examinations were within normal limits. Ophthalmic examination revealed bilateral anterior lenticonus and central thin posterior subcapsular cataract with oil droplet reflex and normal fundus. ENT evaluation revealed bilateral moderate sensorineural hearing loss. Investigations: Case2 14 years old male born to parents of second degree consanguinous marriage admitted with complaints of facial puffiness and swelling of legs for 1week. He had history of hearing impairment since 7 years of age. He gives history of hematuria for 4 days following upper respiratory tract infection 2 years back. His maternal uncle who had similar complaints and underwent multiple hemodialysis died at the age of 32 years.

Complete blood count	Normal
Blood urea	93
Serum creatinine	3.4
Serum electrolytes	Normal
Urine analysis	
Albumin	+++
RBCs	Plenty
24 hour urine protein	900mg
Serum protein and albumin	Normal
Serum complement c3 c4	Normal
ASO titre	Normal
Ultrasonogram	Normal sized kidneys with increased cortical echoes

On examination he had facial puffiness and pedal oedema. Vitals were stable and system examinations were within normal limits. Ophthalmic examination revealed bilateral anterior lenticonus (fig 1) with oil droplet reflex and normal fundus. ENT evaluation revealed bilateral moderate sensorineural hearing loss. Investigations

Complete blood count	Normal
Blood urea	74
Serum creatinine	2.2
Serum electrolytes	Normal
Urine analysis	
Albumin	Loaded
RBCs	10-12/hpf
24 hour urine protein	1850mg
Serum protein and albumin	Normal
Serum complement c3 c4	Normal
ASO titre	Normal
Ultrasonogram	Normal sized kidneys with increased cortical echoes

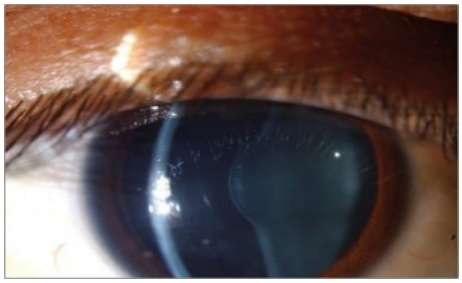

Fig.1 Anterior lenticonus

Three out of the below four criteria establishes the diagnosis of Alport syndrome:[4] 1) Family history of hematuria, progressing to ESRD 2) Thickening and splitting of the glomerular basement membrane 3) Sensorineural deafness 4) Anterior lenticonus or perimacular flecks[5] With the above criteria we have diagnosed Alport syndrome in these cases. 80-85% cases of Alport syndrome are inherited as X- linked recessive condition

In this case series we present an adolescent female with renal failure, which is rare. Moreover these cases highlight the Importance of family history, ophthalmic and ENT evaluation In a young patient presenting with hematuria and abnormal renal parameters or urine analysis .

Discussion

Basement membranes are composed of type IV collagen and are made of chains 1 – 6 located at various sites encoded by the following genes[1,2,3] *COL4A1* and *COL4A2* chr 13
COL4A3 and *COL4A4* chr 2
COL4A5 and *COL4A6* X chr

1 and 2 chains all basement membranes3 and 4 chains basement membranes of the glomerulus, cochlea, and eye5 chain glomerulus, cochlea, eye, and epidermis

Alport syndrome is the result of mutations in *COL4A3, COL4A4,* or *COL4A5* with consequent abnormalities in the basement membranes of the glomerulus (leading to hematuria, glomerulosclerosis, and ESRD), cochlea (causing deafness), and eye (resulting in lenticonus and perimacular flecks)[1,2,3,4,5]. XLAS – (80% - 85%) mutations of the alpha-5 chain [gene COL4A5] ARAS – (10% - 15%) mutations in both the copies of alpha-3 or alpha-4 chains [genes COL4A3 or COL4A] ADAS – (5%) mutations in the alpha-3 or alpha-4 chains [genes COL4A3 or COL4A4][4] Renal biopsy shows glomerular basement membrane thinning, spliting or thickening detected by electron microscopy. Specimen can also be tested for type IV collagen -3, -4 and -5 chains (COL4A3, COL4A4, COL4A5). This confirms the diagnosis of Alport Syndrome and can usually determine the genetic form of the disease (XLAS, ARAS, or ADAS) [2,4] Skin biopsy can be done when XLAS (X-linked Alport Syndrome) is suspected as type IV collagen alpha-5 chain (COL4A5) is normally present in skin also.[7] Immunohistochemistry evidence of the XLAS may be obtained from biopsies of either the skin or the renal glomerulus. Antibodies are used to detect the presence or absence of the 3, 4, and 5 chains of collagen type 4. All three of these alpha chains are present in the glomerular basement membrane of normal individuals. In individuals expressing the X-linked form of Alport syndrome, however, the presence of the dysfunctional 5 chain causes the assembly of the entire collagen 4 complex to fail, and none of these three chains will be detectable in either the glomerular or the renal tubular basement membrane. Only 5 is normally expressed in the skin, so in XLAS on a skin biopsy there is absence of 5 staining.[4,7] No treatment prevents the progression to end-stage renal disease in male patients with X-linked Alport syndrome or in patients with autosomal recessive disease. ACE inhibitors

decrease proteinuria and may slow the rate of progression to ESRD).[8] Cyclosporine can be tried but it may accelerate the development of interstitial fibrosis due to calcineurin-induced nephrotoxicity. Renal replacement therapy(RRT) is indicated as renal failure advances. Patient survival on RRT is better when compared to other causes of renal failure.[9] However renal transplantation can place the patient at risk for development of anti glomerular basement membrane disease. Patients without any kidney function problems should be monitored annually, those with moderate kidney function should be monitored every 6 months, and those with advanced kidney failure should be monitored every 1 to 3 months. Patients with Alport Syndrome should also avoid nephrotoxic drugs. Hearing and vision should also be monitored every one to two years beginning in children at 6 to 7 years of age and continued regularly.[8] Most patients with Alport syndrome present with persistent microscopic hematuria and episodic gross hematuria during the first 2 decades of life. The degree of proteinuria is predictive of the rate of progression.

The renal prognosis for male patients with X-linked Alport syndrome and for all patients with autosomal recessive disease is poor, with most progressing to ESRD. Patients with a family history of juvenile-type Alport syndrome or with early onset deafness and ocular changes typically progress to ESRD by age 20-30 years. Male patients with the typical X-linked disease have a renal half-life of about 25 years, and about 90% develop ESRD before age 40 years. The long-term prognosis for female patients with X-linked Alport syndrome is generally more benign than that of male patients, with many surviving to old age with clinically mild renal disease. Observations have shown that as many as 12% of female patients also develop ESRD by age 40 years; this rate increases to 30% by age 60 years and 40% by age 80 years. Among female patients, risk factors for the progression to ESRD include the degree of proteinuria and hearing loss.[2,6]

Bibliography

1. Harrison's Principles of Internal Medicine 18th edition
2. Brenner and Rector's The Kidney 8th edition
3. Kashtan C; "Alport syndrome: An inherited disorder of renal, ocular, and cochlear basement membranes"; Medicine (Baltimore); Sep 1999
4. Hanson H, Storey H, Pagan J, Flinter F; "The Value of Clinical Criteria in Identifying Patients with X-Linked Alport Syndrome"; Clinical Journal of American the Society of Nephrology; Jan 2011
5. Colville DJ, Savige J; "Alport syndrome: A review of the ocular manifestations"; Ophthalmic genetics; Dec 2012
6. Rheault MN; "Women and Alport syndrome"; Pediatric Nephrology; Jan 2012
7. Wang F, Zhao D, Ding J, Zhang H, Zhang Y, Yu L, Xiao H, Yao Y, Zhong X, Wang S; "Skin Biopsy Is a Practical Approach for the Clinical Diagnosis and Molecular Genetic Analysis of X-Linked Alport Syndrome"; Journal of molecular diagnostics; Nov 2012
8. Kashtan C, Ding J, Gregory M, Gross O, Heidet L, Knebelmann B, Rheault M, Licht C; "Clinical practice recommendations for the treatment of Alport syndrome: A statement of the Alport Syndrome Research Collaborative"; Pediatric Nephrology; Mar 2012
9. Temme J, Kramer A, Jager KJ, Lange K, Peters F, Müller GA, Kramar R, Heaf JG, Finne P, Palsson R, Reisæter AV, Hoitsma AJ, Metcalfe W, Postorino M,Zurriaga O, Santos JP, Ravani P, Jarraya F, Verrina E, Dekker FW, Gross O; "Outcomes of Male Patients with Alport Syndrome Undergoing Renal Replacement Therapy"; Clinical Journal of American the Society of Nephrology; Sep 2012