IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 12 Ver. 5 (December. 2018), PP 01-05
www.iosrjournals.org

Alport Syndrome in Kenya: Case Reports and Literature Review

Samuel K. Kabinga[1], Doris W. Kinuthia[2]
[1](College of Health Sciences, East African Kidney Institute, University of Nairobi, P.O. Box 30197 postal code 00100, Nairobi-Kenya)
[2](Department of Paediatrics, Aga Khan University Hospital, Nairobi, P. O. Box 30270 postal code 00100, Nairobi-Kenya)
Corresponding Author: Samuel K. Kabinga

Abstract: *Alport syndrome (AS) is an inherited disorder of basement membranes. It results from mutations affecting specific proteins of the type IV (basement membrane) collagen family. This condition affects the kidneys, the eyes, the hearing, among others. The renal component of the Alport syndrome manifests as hematuria and/or proteinuria, with progressive chronic renal failure, while the ears involvements presents occasionally as high-tone sensorineural hearing loss. The condition manifests with progressive impairment of the affected organs. Renal failure is a major manifestation .Early diagnosis and symptomatic management are key especially in delaying the renal failure. There is paucity of data from Africa about Alport syndrome. We present three cases managed in our hospitals in Kenya, East Africa, literature review and treatment*

Date of Submission: 27-11-2018 Date of acceptance: 10-12-2018

I. Introduction

Alport syndrome (AS) is an inherited disorder of basement membranes. It results from mutations affecting specific proteins of the type IV (basement membrane) collagen family. This condition affects the kidneys, the eyes, the hearing, among others. The renal component of the Alport syndrome manifests as hematuria and/or proteinuria, with progressive chronic renal failure, while the ears involvements presents occasionally as high-tone sensorineural hearing loss. The ocular lesions include anterior lenticonus [1] and retinal fleck. This condition was first identified in a British family by Dr Cecil A Alport in 1927, though it was William Howship Dickinson who made significant contributions for diagnostic characterisation of the disease as he proposed criteria to establish the diagnosis [2, 3].

Gregory et al proposed that at least 4 of the 10 criteria should be fulfilled for a diagnosis of AS. The criteria include:- A family history of nephritis in a first-degree male relative linked to the index case, a history of persistent haematuria, bilateral sensorineural hearing loss involving higher frequencies, widespread glomerular basement membrane ultrastructural abnormalities. Other criteria include ocular findings such as anterior lenticonus and retinal flecks, mutation in collagen type IV alpha (COL4A) gene, immunohistochemical evidence of partial or complete loss of Alport epitope, gradual progression to ESRD in at least relatives of index case, macrothrombocytopenia and diffuse leiomyomatosis [17]. Immunofluorescence staining of basement membranes, electron microscopy of tissues and genetic testing aid in diagnosis too. High index of suspicion, with focused medical and family history are key in making early diagnosis.

II. Cases

Case 1

N.P., 8 year-old male of Ethiopian descent, residing in Kenya, presented in February 2012 with recurrent urinary tract infections. He had been diagnosed with posterior vesico-ureteric valves which were resected in 2012. He had a history of haematuria since the age of two and a half year. He had normal prothrombin time index and normal international normalized ratio. Renal ultrasound scan performed in February 2012 showed right kidney size measurements of 6.06 cm X 3.22 cm, left kidney 6.02 cm X 3.3 cm a small capacity bladder of 47 mL. Hearing assessment in March 2012 revealed normal tympanic membrane and normal hearing thresholds. His mother reported that her brother (N.P. maternal uncle) suffered from kidney disease and was deaf; sister (N.P. maternal aunt) had haematuria. N.P mother reported that she had other close relatives with haematuria who resided in the United Kingdom. Some investigations performed on N.P, his younger brother and his mother are as shown in the table 1, table 2 and table 3.

Case 2

B.K, 15 year-old male had developed deafness at the age of 8 years. He had been diagnosed with right hydronephrosis and left vescicoureteric reflux in September 2011. He had posterior urethral valves resected 2012. He presented with complains of haematuria and suprapubic pains for one and a half years. No fevers. BK was normatensive, with unremarkable systemic examination findings. He had normal echo and electrocardiograms, and normal kidney, ureters and bladder ultrasonigraphic findings. A diethylenetriamine tetraacetic acid scan performed in April 2014 reported a glomerular filtration rate of 88 mL/min. The left kidney contributed 42.7 mL/min (49%), right 45.3 mL/min (51%). No vesicoureteric reflux seen demonstrated. Kidneys, ureters and bladder ultrasound scan performed in April 2015 reported kidneys with normal corticomedullary differentiation, homogenous cortical echogenecity. No calculus or mass seen. There was no hyronephrosis. Right kidney measured 10.1cm X 4.26 cm, left kidney 9.98cm X 5.41 cm. Premicturation volume of 357 mL and post-micturation volume 8.52 mL. He had been on enalapril for proteinuria. His elder brother, K.G., aged 21year currently, developed deafness, haematuria, and end stage renal disease, by June 2011, and currently on chronic intermittent haemodialysis. Mother had history of haematuria. Investigations performed are as shown in tables 1, 2 and 3.

Case 3

T .N., 10 year-old male, suffered from impaired healing, dumb, with squits from childhood. He had been admitted to hospital six times previously since birth. In 2007, he was treated for sputum negative pulmonary tuberculosis for six months, based on haemoptysis and suggestive chest radiographs, with negative sputum for acid-alcohol fast bacilli. The treatment was repeated in 2008. He had been on follow up in eye hospital for squints since 2016. He suffered from chronic kidney disease and was commenced haemodialysis at the Aga Khan University hospital from January 2017. He was admitted in the Kenyatta National Hospital in July 2017 with an episode of sepsis and had been on ng intermittent haemodialysis twice weekly. Abdominopelvic ultrasound scan in September 2017 reported small atrophic kidneys. Right kidney 5.63 cm X1.73 cm, left kidney 5.74 cm X 2.54 cm. Normal urinary bladder, normal liver and pancreas. Chest X-rays in September 2017 was normal. Other investigations are as shown in the tables 1, 2 and 3. He was enrolled in kidney transplantation evaluation programme in September 2017.

Table 1: Urine analyses of NP, brother and mother, BK, brother and TN.

Initials	Date	Specific Gravity	Blood	Protein	Leucocytes	Microscopy
N.P	21/02/12	1030	++	Nil	Nil	RBC-Numerous
	10/12/13	1005	++	Nil		RBC- Numerous No growth obtained
N.P Brother	17/03/12	1010	++	Nil	+	RBC- Numerous Bacteria + No growth
	10/12/13	1025	++++	+++	Nil	RBC-Numerous Bacteria ++++ No growth
N.P mother	17/03/12	1000	++	++	+	RBC- 4-6 amorphous Urate cystals +++ others- Nil No growth
BK	26/01/2012	1030	+++	++	+	RBC 4-5 Bacteria ++ Culture: No growth
BK	17/04/2015	1020	++++	+++	Nil	RBC 15-20 Bacteria - Scanty
TN	14/07/17	1.005	+	++	++	WBC- 12-14 RBC-0-2 Epithelial- 2-4 Bacteria - +
TN	24/07/17	1.015	++	++	Nil	

RBC- Red Blood Cells, WBC- White Blood Cells

Table 2: Serum urea, electrolytes and creatinine for NP, brother and mother, BK, brother and TN.

Initials	Date	Na (136-145 mmol/l)	K (3.3-5.4 mmol/l)	Creatinine (58-96 µmol/l)	Urea (2.1-7.1 mmol/l)
N.P	21/02/12	140	4.2	28	8.9
N.P Mother	17/03/2012	138	4.41	62.0	3.10
N.P brother	17/03/12	140	4.45	45.0	4.30

	10/12/17	139	4.25	31.0	5.10
BK	26/01/2012	139.17	4.01	53.71	6.44
BK	27/04/2015	130	3.44	64	4.0
TN	15/07/2017	131	4.9	743	27.7
TN	16/07/2017	125	4.9	842	41.3
TN	23/10/2017	136	5.6	644	35
TN	01/11/2017	142	5.2	602	31.5
TN	04/05/2018	144	7.07	540	20.5

Table 3: Full blood counts for NP, brother and mother, BK, brother and TN.

Initials	**Date**	**WBC (4.00-10.00 X10^9/l**	**Neutr (45-75%)**	**Lympho (25-40%)**	**RBC (3.80-5.80X10^{12}/l)**	**HB ((11.50-16.50 g/dl)**	**MCV (77.00-93.00fl)**	**Plt (150-450 X 10^9/l)**
N.P	17/03/17	11.02	74.2	19.20	4.37	12.80	87.60	235
N.P. brother	18/03/12	17.67	55.90	33.90	5.63	14.20	72.80	445
NP Mother	10/12/13	13.06	48.8	37.70	5.33	14.20	72.00	312
BK	26/01/12	4.86	46.10	38.10	5.39	14.90	80.70	309
BK	22/04/15	5.48	44.50	43.90	5.23	15.73	87.38	366
TN	15/07/17	8.71	39.6	47.1	3.84	9.3	77.3	267
TN	31/10/17	6.10	29.7	57.0	3.47	8.5	82.7	315
TN	15/09/17	14.35	82.7	11.3	3.57	8.8	76.8	214
TN	04/05/18	7.33	26.2	45	3.23	83.9	83.9	218

WBC- White Blood Cells, Neutr- Nutrophils, Lympho – Lyn]mphocytes, RBC- Red Blood Cells, HB – Haemoglobin, MCV- Mean Corpuscular Volume, Plt - platelets

III. Literature Review and Discussion

Introduction

Alport syndrome (AS) is an inherited disorder of basement membranes. It results from mutations affecting specific proteins of the type IV (basement membrane) collagen family. This condition affects the kidneys, the eyes, the ears, among others. The renal component of the AS manifests as hematuria and/or proteinuria, with progressive chronic renal failure, while the ears involvements presents occasionally as high-tone sensorineural hearing loss. The ocular lesions include anterior lenticonus [1] and retinal fleck. This condition was first identified in a British family by Dr Cecil A Alport in 1927, though it was William Howship Dickinson who made significant contributions for diagnostic characterisation of the disease as he proposed criteria to establish the diagnosis [2, 3]. In our cases, the patients and the reported family members had presentations consistent with AS.

Pathology and presentation of Alport syndrome

Alport syndrome results from inherited defects in genes which code for specific collagen. Chromosomes 2, 13 and X are involved. Specifically, the collagen type IV (COL4) is affected, which is a major constituent of basement membranes (BM). There are six isomeric chains of collagen type IV, designated as α1(IV) to α6(IV). Each type IV collagen molecule is a heterotrimer composed of three α chains. There are at least three types of type IV collagen heterotrimer: α1(IV)2–α2(IV), α3(IV)–α4(IV)–α5(IV), and α5(IV)2–α6(IV). The abnormalities in the collagen result thin basement membrane. There are no standard criteria for defining the lower limit for normal GBM thickness below which the GBM can be considered thin, and there is considerable variability between the values established as this lower limit at different centres [15]. However, Dische *et al* using the orthogonal intercept/mean harmonic thickness method of GBM measurement, established a normal range of GBM thickness in adults of 330nm to 460 nm, and they defined thin GBM nephropathy as an average GBM thickness of less than 330 nm [16].

Alport syndrome (AS) is a disease of ultrastructural collagen abnormality. This abnormality is also a rare cause of end-stage renal disease (ESRD) [4, 5]. In our cases, only T.N. had developed ESRD by the age of 10, while B.K. brother was reported to have developed ESRD by the age of 14. The genetic basis for AS results in mutations in the collagen type IV alpha 3 chain (COL4A3), collagen type IV alpha 4 chain (COL4A4), and collagen type IV alpha 5 chain (COL4A5). Approximately 4 in every 5 AS cases are caused by X-linked mutations in the collagen type 4 alpha 5 chain (COL4A5) gene encoding type IV collagen alpha 5 (α5) chain [1, 6]. Males with X-linked AS progress inexorably to ESRD, with ESRD risks of 50% by age 25 years, 90% by age 40 years, and nearly 100% by age 60 years [1]. Age at ESRD is strongly correlated with COL4A5 genotype in males with X-linked Alport syndrome (XLAS) [1–3]; risk of ESRD by age 30 is 90% for deletions and nonsense mutations of COL4A5, 70% for splicing mutations, and 50% for missense mutations [7-9]. Women are rarely affected except in cases of lyonisation of sex chromosomes in an X-linked inheritance (XLAS), which is the most common type (85%). In the rarer autosomal recessive Alport syndrome (ARAS) or autosomal dominant Alport syndrome (ADAS), both sexes are equally affected. Women are less frequently affected with

sensori-neural hearing loss [10]. In females with XLAS, clinical features are generally milder, because of X chromosome inactivation. About 15% develop renal failure by the age of 60 years, and rarely, the lenticonus or central retinopathy [11].

In XLAS, mutations in the COL4A5 gene results in the replacement of the collagen IV $\alpha 3\alpha 4\alpha 5$ network with the $\alpha 1\alpha 1\alpha 2$ heterotrimer. Affected membranes may also possess ectopic laminin and increased matrix metalloproteinase levels, which makes them more susceptible to proteolysis. Mechanical stress, due to the less elastic membrane and hypertension, interferes with integrin-mediated podocyte–glomerulobasement membrane (GBM) adhesion too. Proteinuria occurs when urinary levels exceed tubular reabsorption rates, and initiates tubulointerstitial fibrosis. The glomerular mesangial cells produce increased transforming growth factor beta (TGFβ) and connective tissue growth factors (CTGF) which also contribute to glomerulosclerosis [12]. Haematuria occurs through breaks in the GBM [13]. Patients with autosomal dominant Alport syndrome (ADAS) show nonspecific clinical manifestations, except for hematuria at a young age. The renal phenotype of ADAS is much milder than that of autosomal recessive Alport syndrome (ARAS) or XLAS men [14].

Diagnosis of Alport syndrome

Gregory et al proposed that at least 4 of the 10 criteria should be fulfilled for a diagnosis of AS. The criteria include:- A family history of nephritis in a first-degree male relative linked to the index case, a history of persistent haematuria, bilateral sensorineural healing loss involving higher frequencies, widespread glomerular basement membrane ultrastructural abnormalities. Other criteria include ocular findings such as anterior lenticonus and retinal flecks, mutation in collagen type IV alpha (COL4A) gene, immunohistochemical evidence of partial or complete loss of Alport epitope, gradual progression to ESRD in at least relatives of index case, macrothrombocytopenia and diffuse leiomyomatosis [17]. The patient N.P., his brother and mother had haematuria. The maternal uncle and aunt to N.P. were reported to have suffered from haematuria and the uncle was deaf and suffered from ESRD.

B.K. suffered from chronic haematuria and is deaf. His elder brother (K.G.) suffered from haematuria, and ESRD, and is currently on haemodialysis. In the case of T.N, he was deaf and developed ESRD by the age of 10. He had a history of haematuria, though no family history of haematuria, ESRD or deafness was reported. Immunofluorescence staining of basement membranes, electron microscopy of tissues and genetic testing aid in diagnosis too.

Treatment

Delaying development of ESRD in patients with AS focus on the early introduction of renin-angiotensin system (RAS) blockade to reduce urinary protein excretion [18, 19]. Consensus recommendations for the management of AS children include:-early screening for haematuria in at-risk children, regular determination of urinary protein excretion on diagnosis, and initiation of RAS blockade once overt proteinuria develops [18]. Treatment with angiotensin converting enzyme (ACE) inhibitors delays renal failure progression by reducing intraglomerular hypertension, proteinuria, and fibrosis [12], and improves life expectancy in a time-dependent manner [20]. Antifibrotic, a reduction in blood pressure puts less stress on the defective GBM, on the adjacent podocyte, and on the whole glomerulus. Dialysis and renal transplantation in end-stage disease are effective and relatively safe [21]. Alport syndrome patients experienced comparable dialysis and renal transplant outcomes to matched non-Alport end-stage renal disease controls in the contemporary cohort [22]. Patients with AS have the risk of anti-GBM nephritis post kidney transplantation though anti-GBM nephritis is not a common aetiology of rejection [23]. Though patients with AS as the cause of ESRD have a better survival on haemodialysis (HD) compared with patients on ESRD due to other conditions on HD, they also appear to have superior patient and graft survival after deceased-donor kidney transplantation compared with patients receiving RRT because of other causes of kidney failure [24].

IV. Conclusion

In conclusion, Alport syndrome is not uncommon in this part of the world. Careful history including targeted family history for children and females presenting with haematuria are important. Early recognition and early initiation of symptomatic treatment may delay development of ESRD.

References

[1]. Baikara, B.T., et al., A Novel Mutation in a Kazakh Family with XLinked Alport Syndrome. PLoS ONE, 2015. **10**(7): p. e0132010.
[2]. Alport, A.C., Hereditary familial congenital haemorrhagic nephritis. BMJ (London), 1927. **1**: p. 504-506.
[3]. Lagona, E., et al., Skin biopsy for the diagnosis of Alport syndrome. Hippokratia, 2008. **12**: p. 116-118.
[4]. Heidet, L. and M.C. Gubler, The renal lesions of Alport syndrome. J Am Soc Nephrol, 2009. **20**: p. 1210-1215.
[5]. Williamson, D.A., Alport syndrome of hereditary nephritis with deafness. Lancet, 1961. **2**: p. 1321-1323.
[6]. Hudson, B.G., et al., Alport's syndrome,Goodpasture's syndrome, and type IV collagen. N Engl J Med, 2003. **348**: p. 2543-2556.
[7]. Jais, J.P., et al., X-linked Alport syndrome:natural history in 195 families and genotype-phenotype correlations in males. J Am Soc Nephrol, 2000. **11**: p. 649-657.

[8]. Gross, O., et al., Meta-analysis of genotype-phenotype correlation in X-linked Alport syndrome: impact on clinical counseling. Nephrol Dial Transpl, 2002. **17**: p. 1218-1227.
[9]. Bekheirnia, M.R., et al., Genotype-phenotype correlation in X-linked Alport syndrome. J Am Soc Nephrol, 2010. **21**: p. 876-883.
[10]. Ghosh, S., et al., Alport syndrome: a rare cause of uraemia. BMJ Case Rep, 2014. **Online**.
[11]. Jais, J.P., et al., X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study. J Am Soc Nephrol, 2003. **14**: p. 2603-2610.
[12]. Savige, J., Alport syndrome: its effects on the glomerular filtration barrier and implications for future treatment. J Physiol, 2014. **592**(18): p. 4013-4023.
[13]. Collar, J.E., et al., Red cell traverse through thin glomerular basement membranes. Kidney Int, 2001. **59**: p. 2069-2072.
[14]. Kamiyoshi, N., et al., Genetic, Clinical, and Pathologic Backgrounds of Patients with Autosomal Dominant Alport Syndrome. Clin J Am Soc Nephrol, 2016. **11**: p. 1441-1449.
[15]. Haas, M., Alport Syndrome and Thin Glomerular Basement Membrane Nephropathy A Practical Approach to Diagnosis. Arch Pathol Lab Med, 2009. **133**: p. 224-232.
[16]. Dische, F.E., Measurement of glomerular basement membrane thickness and its application to the diagnosis of thin-membrane nephropathy. Arch Pathol Lab Med, 1992. **116**: p. 43-49.
[17]. Gregory, M.C., et al., Alport syndrome-clinical phenotypes,incidence, and pathology. Contrib Nephrol, 1996. **117**: p. 1-28.
[18]. Kashtan, C.E., et al., Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport syndrome research collaborative. Pediatr Nephrol, 2013. **28**(1): p. 5-11.
[19]. Savige, J., et al., Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. J Am Soc Nephrol, 2013. **24**(3): p. 364-375.
[20]. Gross, O., et al., Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. Kidney International, 2012. **81**: p. 494-501.
[21]. Wyss, H.M., et al., Biophysical properties of normal and diseased renal glomeruli. Am J Physiol Cell Physiol, 2011. **300**: p. 397-405.
[22]. Mallett, A., et al., End-stage kidney disease due to Alport syndrome:outcomes in 296 consecutive Australia and New Zealand Dialysis and Transplant Registry cases. Nephrol Dial Transplant, 2014. **29**: p. 2277-2286.
[23]. Mojahedi, M.J., R. Hekmat, and H. Ahmadnia, Kidney Transplantation in Patients With Alport Syndrome. Urol J, 2007. **4**: p. 234-237.
[24]. Temme, J., et al., Outcomes of Male Patients with Alport Syndrome Undergoing Renal Replacement Therapy. Clin J Am Soc Nephrol, 2012. **7**: p. 1969-1976.

Samuel K. Kabinga. "Alport Syndrome in Kenya: Case Reports and Literature Review"." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 12, 2018, pp 01-05.