Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2021;11:308–313
DOI: 10.1159/000519076
Received: April 26, 2021
Accepted: August 9, 2021
Published online: October 11, 2021

Case Series

A Case Report of *COL4A5* Gene Mutation Alport Syndrome in 2 Native African Children

Emmanuel Oduware[a] Nosakhare Joyce Iduoriyekemwen[b]
Michael Ibadin[b] Henry Aikhionbare[b]

[a]Department of Family Medicine, University of Benin Teaching Hospital, Benin City, Nigeria;
[b]Department of Child Health, University of Benin/University of Benin Teaching Hospital, Benin City, Nigeria

Keywords
Alport syndrome · *COL4A5* gene mutation · Children

Abstract
Alport syndrome is a heterogeneous genetic disease involving the basement membrane of the glomeruli, inner ear, retina, and lens capsule. It typically manifests as progressive glomerulopathy that frequently results in end-stage renal disease, high-tone sensorineural deafness, and ocular abnormalities of anterior lenticonus and yellow and white dots and flecks on the macular of the retina. In this report, we describe the cases of 2 siblings: 15- and 13-year-old boys of pure African descent with the *COL4A5* gene mutation. Both children had the classical features of Alport syndrome haematuria, proteinuria, progressive sensorineural high-tone hearing loss, and ocular abnormalities. Their renal abnormalities initially regressed on therapy with angiotensin-converting enzyme inhibitors but reoccurred, depicting the need for early diagnosis as the early institution of this therapy before significant glomerulopathy is advocated.

Introduction

Alport syndrome, a major familial disorder hallmarked by haematuria [1], is a heterogeneous genetic condition characterized by progressive renal damage, sensorineural deafness, and ocular abnormalities. The abnormalities result from mutation(s) of genes

Correspondence to:
Nosakhare Joyce Iduoriyekemwen, nosaiduos2006@yahoo.com

Case Rep Nephrol Dial 2021;11:308–313
DOI: 10.1159/000519076

encoding the alpha chains: α3, α4, and α5 type IV collagen, which are the most vital structural components of basement membranes (BMs), especially that of the kidney, as well as the cochlear and the eye [2]. These cases are of interest because of the rarity of such conditions, especially in our locale. Available published reports in Nigeria are in adult population only [3, 4]. Furthermore, the extant case report highlights the importance of early diagnosis.

Case Presentation

Case 1

Case 1 is that of a 15-year-old male who presented with hearing difficulty and poor vision that were noticed 3 years earlier. The symptoms had worsened with time. He also had facial and bilateral lower leg swellings of 2-week duration at initial presentation. There was no history of gross haematuria, but his younger sibling had similar features while his maternal grandmother had cataract as a young woman. Parental consanguinity was absent. He was referred from the General Practice Clinic of the University of Benin Teaching Hospital, where he was initially seen.

Examination following referral revealed that the patient was oedema free, heart rate was normal (76 beats/min regular), and blood pressure was normal (100/60 mm Hg less than the 50th percentile for age and height). Examination of the respiratory system showed no abnormal findings. Urinalysis revealed massive proteinuria (++++), haematuria (+++), normal white blood cell count (5.9 × 10^3/μL), haemoglobin (12.8 g/dL), and platelet count 178 × 10^9/L. Peripheral blood film showed anisopoikilocytosis and burr cells, but no leukocyte inclusion bodies. His serum electrolyte, urea, and creatinine levels were normal (urea, 19 mg/dL; serum creatinine, 0.7 mg/dL; and estimated glomerular filtration rate [eGFR], 105.0 mL/min/1.73 m^2). Renal ultrasound revealed enlarged kidneys (dimensions: 12.5 cm × 4.7 cm on the right and 12.5 cm × 5.1 cm on the left) with mild parenchymal echogenicity with some loss of corticomedullary differentiation. Pure tone audiometry revealed bilateral moderate sensorineural hearing loss. Slit-lamp examination revealed keratoconus and immature cataract of the right eye that was also confirmed on ocular ultrasound. He also had amblyopia. Genetic analysis revealed a pathogenic variant of the *COL4A5* gene (NM_033380.3: exon 44: c.3883C>T: p.Gln1295* nonsense variant). The genetic analysis was carried out at the SYNLAB Medizinisches Versorgungszentrum Human Genetic laboratory in Munich, Germany. All 3 genes were investigated: *COL4A3* (NM_000091.5), *COL4A4* (NM_000092.5), and *COL4A5* (NM_033380.3). Following extraction of genomic DNA from peripheral blood nucleated cells, coding regions and adjacent intronic regions (±10 bp) were analysed using the *sequencing by synthesis* method performed using the *NextSeq 550* system (Illumina). However, regions with a coverage of <20× were analysed by Sanger sequencing. Alignment and the analysis of variants were performed using the Seq/Next-module of the SeqPilot by Medisys Software (version 4.3.1 Build 506) compared to the human reference genome hg19/GRCh37. The analysis for deletions or duplications was carried out with the Varvis software module (version 1.10.0), and findings were verified using multiple ligation-dependent probe amplification. The variant was classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

His proteinuria is being treated with an angiotensin-converting enzyme inhibitor (ACEI) while hearing aid and corrective glasses have been prescribed. He is on regular follow-up at the Paediatric Nephrology Clinic. There was significant reduction in proteinuria and haematuria initially but had rebound proteinuria 8 months into treatment. Currently, his urinary albumin-to-creatinine ratio (ACR) is 732.5 mg/mmol.

Case Rep Nephrol Dial 2021;11:308–313
DOI: 10.1159/000519076

Case 2

Case 2 is that of a 13-year-old boy, the younger sibling of the case reported as case 1. He presented with hearing difficulty and poor vision that started 5 years earlier. Symptoms have worsened with time. He also did not have a history of gross haematuria.

On examination, the patient had no oedema. The heart rate was normal (80 beats/min) and regular. He also had normal blood pressure (90/60 mm Hg less than the 50th percentile for age and height). Slit-lamp examination was normal. He, however, had amblyopia.

Urine examination revealed massive proteinuria (+++) and haematuria (+++). He, however, had normal haemoglobin level (13.1 g/dL), normal white blood cell count (10.5 × 10^3/μL), and normal platelet count 240 × 10^9/L. Peripheral blood film showed anisopoikilocytosis and burr cells, but no leukocyte inclusion bodies. His serum electrolyte, urea, and creatinine values were also normal (urea, 17 mg/dL; serum creatinine, 0.6 mg/dL, and eGFR, 106.7 mL/min/1.73 m^2). Ultrasonography revealed a normal-sized kidney (10.7 cm × 3.4 cm on the right and 10.6 cm × 4.3 cm on the left). Renal parenchyma showed normal echogenicity but a loss of corticomedullary differentiation. Pure tone audiometry revealed bilateral moderate sensorineural hearing loss. However, genetic analysis was not done because of financial constraints.

Glasses and hearing aid have been prescribed for the patient. He is also being treated with an ACE inhibitor and on follow-up at the Paediatric Nephrology Clinic. A remarkable reduction in proteinuria was observed initially, but he also had reoccurrence after 8 months of treatment. His most recent urinary ACR is 199.4 mg/mmol.

Evaluation of Their Mother

Their mother was also evaluated, and she was observed to have proteinuria, haematuria, serum creatinine 0.6 mg/mL, and eGFR 136 mL/min/1.73 m^2, but unimpaired hearing and vision. Her most recent urinary ACR is 5.9 mg/mmol.

Discussion

Alport syndrome is a genetic disease involving the BM of the glomeruli, inner ear, retina, and lens capsule. It typically manifests as progressive glomerulopathy (haematuria and proteinuria) that frequently culminates in end-stage renal disease (ESRD), high-tone sensorineural deafness, and ocular abnormalities of anterior lenticonus and yellow and white dots and flecks on the macular and mid-peripheral area of the retina [1, 2]. Pathologic variants can result from mutation of any of the 3 genes encoding for the heterotrimeric alpha chains: α3, α4, and α5 components of collagen type IV that are exclusively found on podocytes of mature glomerular BMs, basilar membrane and BM of stria vascularis, spinal limbus, prominence of the cochlea, anterior lens capsule, and Descemet and Bruch membranes of the eyes [2]. The varied involvement of these cells explains the heterogeneity of the disorder.

COL4A3 and *COL4A4* genes, located on chromosome 2q36, encode the alpha chains α3 and α4, respectively. Homozygous and heterozygous mutations in these genes are expressed as autosomal disease [5]. The autosomal recessive Alport syndrome variant is found in 15% of individuals of at risk families, while the rare autosomal dominant Alport syndrome variant is seen in 5% of individuals of at risk families [1, 2, 6]. However, more recent studies using next-generation sequencing analysis report that autosomal dominant Alport syndrome accounts for up to 20–30% of Alport syndrome [7]. The *COL4A5* gene located on the long arm of chromosome X encodes for the α5 chain. Mutations in the *COL4A5* gene are expressed as X-linked inheritance. These individuals have the X-linked dominant Alport syndrome (XLAS) variant, which was initially reported to occur in 80–85% of families affected [1, 2, 6]. However, recent studies using next-generation sequencing analysis show XLAS accounts for about 65%

Case Rep Nephrol Dial 2021;11:308–313
DOI: 10.1159/000519076

of cases [7]. Several variants of the mutant *COL4A5* gene exist, as there are no hotspots on the large *COL4A5* gene. As at 2019, there were 1,900 variants of the gene reported, with 1,100 unique changes identified [8]. The frequency of occurrence of these variants differs from study to study. Most mutations are missense mutations reported in 35–52% of cases and 15–16% are from splice-site mutations. Large rearrangements with deletions are seen in 9–14% of cases and 5–8% nonsense mutations [9–11]. The genetic analysis of the index patient (case 1) confirmed pathologic mutation in the *COL4A5* gene with a premature stop codon making it a nonsense variant.

Correlation between the genotype and the clinical manifestation and disease severity is clearly observed in males with XLAS [9]. These males have the hemizygous mutation [5], which often manifests all the renal and extrarenal features of the disease, as observed in the discussed cases. They also have the severe form of the disease as they tend to have early-onset ESRD and deafness [2, 5, 6]. Females with XLAS are heterozygotes, and they experience variable clinical presentation and course. This gender disparity in XLAS individuals is believed to occur due to X-inactivation in females [2, 5, 6]. Their disease severity is unrelated to the type of mutation [9, 12]. Severe mutation includes large deletions and rearrangement, frame-shift mutations, and nonsense mutation. These are associated with severe disease with early onset of symptoms [9]. Kashtan et al. [13] reported that ESRD risk by age 30 in males with XLAS was 90% if the mutation is a deletion and nonsense mutation, 70% if splicing mutation, and 50% if missense. The nonsense mutation observed in our index case can explain the early development of nephropathy and hearing loss.

In individuals with Alport syndrome, intra- and inter-familial variabilities are also documented regarding the rate of progression of chronic kidney disease to ESRD [14]. However, the progression rate can be delayed using ACEIs [15]. Commencing ACEI therapy before the onset of proteinuria, that is, early in the course of the illness, is recommended. Studies have shown that pre-emptive therapy is the most effective in delaying renal failure [15]. Hence, early diagnosis of Alport syndrome in early childhood is very essential. Both children at presentation had significant proteinuria. In both patients, proteinuria and haematuria resolved initially following the commencement of ACEI but recurred later. This observed treatment failure probably resulted from the late commencement of therapy, buttressing the fact that early diagnosis and pre-emptive treatment with ACEI are critical in managing Alport syndrome.

A family history of renal disease is a strong diagnostic consideration in Alport syndrome. In XLAS, most mothers of affected boys also have the disease [6]. In the cases discussed, their mother had haematuria and proteinuria (discovered at time of evaluation of the children) but normal hearing and vision. Positive family history of renal disease, early-onset renal failure, hearing loss, and ocular lesions, especially in the absence of parental consanguinity in a male, are highly supportive of the diagnosis of XLAS [6]. However, in up to 15% of cases with XLAS, family history may be negative due to de novo mutation [1, 6]. Genetic testing, therefore, is mandatory in the determination of the specific mode of transmission [2]. However, genetic testing could not be extended to all index case family members due to financial constraints.

Conclusion

This study confirms that Alport syndrome does occur in children of pure African descent. It also shows that therapeutic failure is associated with late presentation, as other studies have reported. Early diagnosis is emphasized as this will facilitate early therapeutic intervention.

Statement of Ethics

This case report adhered to the Declaration of Helsinki, and written informed consent for the investigations and publication was obtained from the patients' mother.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

The authors received no funding for this work.

Author Contributions

N.J. Iduoriyekemwen drafted the article. E. Oduware and H. Aikhionbare revised the article critically for important intellectual content. M. Ibadin revised the article critically for important intellectual content and gave final approval of the version to be submitted.

Data Availability Statement

No datasets were generated or analysed during the current study. However, the clinical information and laboratory investigations cited are domiciled in the medical records of the University of Benin Teaching Hospital, and are not in the public domain in order to protect patients' privacy.

References

1 Kashtan CE. Familial hematuria. Pediatr Nephrol. 2009;24(10):1951–8.
2 Kruegel J, Rubel D, Gross O. Alport syndrome – insights from basic and clinical research. Nat Rev Nephrol. 2013;9:170–8.
3 Oni AO, Eweka AO, Otuaga PO, Odia JO. Alport's syndrome. Saudi J Kidney Dis Transpl. 2009;20(6):1087–9.
4 Ndu VO, Ujah T, Oko-Jaja R. Alport syndrome in a 32-year-old: a case report. Yen Med J. 2020;2(1):173–8.
5 Kashtan CE, Ding J, Garosi G, Heidet L, Massella L, Nakanishi K, et al. Alport syndrome a unified classification of genetic disorders of collagen IV α3,4,5: a position paper of the Alport syndrome classification working group. Kidney Int. 2018;93:1045–51.
6 Savige J, Gregory M, Gross O, Kashtan C, Ding J, Flinter F. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. J Am Soc Nephrol. 2013;24:364–75.
7 Fallerini C, Dosa L, Tita R, Del Prete D, Feriozzi S, Gai G, et al. Unbiased next generation sequencing analysis confirms the existence of autosomal dominant Alport syndrome in a relevant fraction of cases. Clin Genet. 2014;86:252–7.
8 Zhao X, Shang X, Chen C, Liu L, Wang C, Zhao G, et al. Identification of four novel mutations in the COL4A5 gene identified in Chinese patients with X-linked Alport syndrome. Biomed Rep. 2020;13:4.
9 Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, et al. X-linked Alport syndrome: natural history in 195 families and genotype-phenotype corrections in males. J Am Soc Nephrol. 2000;11:649–57.
10 Crockett DK, Pont-Kingdon G, Gedge F, Sumner K, Seamons R, Lyon E. The Alport syndrome COL4A5 variant database. Hum Mutat. 2010;31:E1652–7.
11 NozuK, Takaoka Y, Kai H, Takasato M, Yabuuchi K, Yamamura T, et al. Genetic background, recent advances in molecular biology and development of novel therapy in Alport syndrome. Kidney Res Clin Pract. 2020;39(4):402–13.

Case Rep Nephrol Dial 2021;11:308–313
DOI: 10.1159/000519076

12 Yamamura T, Nozu K, Fu XJ, Nozu Y, Ye MJ, Shono A, et al. Natural history and genotype-phenotype correlation in female X-linked Alport syndrome. Kidney Int Rep. 2017;2:850–5.
13 Kashtan CE, Ding J, Gregory M, Gross O, Heidet L, Knebelmann B, et al. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport syndrome research collaborative study. Pediatr Nephrol. 2013;28:5–11.
14 Matthaiou A, Poulli T, Deltas C. Prevalence of clinical, pathological and molecular features of glomerular basement nephropathy caused by COL4A3 or COL4A54 mutations: a systematic review. Clin Kidney J. 2020;13(6):1025–36.
15 Gross O, Licht C, Anders HJ, Hoppe B, Beck B, Tönshoff B, et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. Kidney Int. 2012;81:494–501.