International Journal of Research in Medical Sciences
Pradhan P et al. Int J Res Med Sci. 2023 Dec;11(12):4531-4534
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20233726

Case Report

An unusual coalition of medullary nephrocalcinosis with a novel genotypic variant of Alport syndrome type-1

Poonam Pradhan, Aritra Kapat*, Asok K. Mandal, Ashok K. Bala

Department of Paediatric Medicine, Dr. B.C. Roy Post Graduate Institute of Paediatric Sciences, Kolkata, West Bengal, India

Received: 12 November 2023
Accepted: 22 November 2023

***Correspondence:**
Dr. Aritra Kapat,
E-mail: doc.kapat@gmail.com

ABSTRACT

Alport's syndrome is a type of inherited disorder of the basement membrane characterized by a spectrum of phenotypes ranging from progressive renal injury to varied extrarenal manifestations comprising auditory and ocular abnormalities. Here in, we present a 3-year-old child born out of nonconsanguineous marriage who presented with fever, intermittent microscopic haematuria, and recurrent gross haematuria, proteinuria with normal auditory brainstem response and ocular slit lamp examination findings. Renal biopsy yielded normal light microscopy and immunofluorescence study whereas minimal changes in the glomerular basement membrane (GBM) collagen were detected on electron microscopy, suggesting possibilities of Alport's syndrome. Ultrasonographic renal imaging yielded the presence of bilateral medullary nephrocalcinosis. Angiotensin converting enzyme inhibitors along with angiotensin receptor blockers were used to curb the disease progression. A final clinical exome sequencing corroborated the phenotype with a diagnosis of Alport's syndrome type-1 linked to a novel pathogenic variant c.1892dup (p.Gly632ArgfsTer2) showing hemizygous single base pair insertion/duplication in COL4A5 gene. To the best of our knowledge, this unusual association of Alport's syndrome with medullary nephrocalcinosis has not been reported worldwide in any previous medical literature making this report a primi one.

Keywords: Alport syndrome, Haematuria, Proteinuria, Nephrocalcinosis

INTRODUCTION

Alports syndrome, the term coined by Cecil A. Alport in 1927, is a hereditary disorder of glomerular basement membrane existing in three forms- X linked dominant (80%), autosomal recessive (15%), autosomal dominant (5%) with an incidence rate 1:5000 where the males are more affected.[1] The genetic variability of Alports is explained by frameshift mutations/single base mutations like inversion/duplication in the alpha 5 chain gene of type IV collagen located in chromosome xq22.[1] Alpha 5 chain primarily targets the glomerular basement membrane attributing to the most common presentation of the disease i.e. haematuria and nephritis ultimately leading to end-stage renal disease.[2] Progressive hearing loss, anterior lenticonus, keratoconus, and cataract are other common extrarenal manifestations reported in the case of classical Alports syndrome.[3] Here in we present a case report of paediatric Alport syndrome with X-linked dominant inheritance without any extrarenal manifestation caused by a novel pathogenic hemizygous single base pair duplicating mutation of COL4A5 gene with a newly found bizarre association of medullary nephrocalcinosis which is first such to be reported worldwide.

CASE REPORT

A 3-year-old first-order child born out of nonconsanguineous marriage presented to the emergency with complaints of with complaints of episodic dark red urination since last 2 months which was insidious in onset along with a history of non-documented on and off fever. There was no history of associated flu like symptoms, gastrointestinal symptoms, skin rash, trauma, any drug

intake, animal bite in the recent past. On further probing the patient seemed to have had three attacks of recurrent urinary tract infections in the past for which the patient was treated on outpatient basis, *Escherichia coli* being the culprit organism on every occasion. There was no history of similar illnesses among parents.

The child was born at term through a normal vaginal delivery with a birth weight of 2.6 kg. The antenatal, natal and postnatal periods were uneventful. The boy has achieved normal developmental milestones in all four domains and is immunised as per age with an apparently normal nutritional history.

On general physical examination the child was alert, conscious, with a Glasgow coma scale of 15/15(E4V5M6), moderate pulse volume, a heart rate of 94/min, mild pallor without any evidence of icterus, cyanosis, clubbing, oedema or localised lymph node enlargement. The office BP recording was more than 95th percentile (120/700, 118/70, 124/72) on three consecutive measurements for the patient.

The baby weighed around 14 kg (between 3rd and 50th percentile), and the height was 103 cm (just below 3rd percentile) and body mass index was 13.4 kg/m^2.

Systemic examinations of neurological, respiratory, gastrointestinal, cardiovascular systems did not have any significant abnormalities.

Management and outcome

An initial urinanalysis revealed a pH of 6.5, specific gravity 1.018, 2+ albuminuria, hematuria (red blood cells >100/HPF), presence of granular casts without any evidence of glycosuria, significant elevation of pus and epithelial cells. To our surprise the hematuria and proteinuria persisted when tested after 7 days and 15 days when the urine colour returned back to normal confirming presence of microscopic hematuria. A complete haemogram revealed mild anaemia as haemoglobin was 9.1 g/dl, total leucocyte count was 8400/cumm with a differential of 42% neutrophil and 47% lymphocytes with a platelet count of 1.9 lakhs/cumm without any evidence of special cells on peripheral blood smear. Liver function test revealed mild hypoalbuminemia of 3 mg/dl with a total protein concentration of 6.3 mg/dl whereas the liver enzymes were absolutely normal. Renal function test was also normal, urea being 36 mg/dl and creatinine being 0.6 mg/dl and urine protein: creatinine ratio being 1.0403. Further electrolyte estimation revealed mild hypercalcemia of 13.7 mg/dl with an apparently normal coagulation profile (prothrombin time being 13.9 second and activated partial thromboplastin time being 27.5 second). Arterial blood gas analysis did not show any evidence of metabolic acidosis and electrolytes level were also normal. Renal ultrasonographic imaging revealed a fortuitous finding of bilateral medullary nephrocalcinosis (Figure 1). Additional investigations led to a borderline elevation of vitamin D as 67 ng/ml with normocalcuria, with spot urinary calcium creatinine ratio being 0.14. Other supplementary workups revealed normal thyroid profile (thyroid stimulating hormone 2.4 mU/l and free T4 1.1 ng/dl), serum uric acid level 5.1 mg/dl, normal complement 3 and complement 4 level, negative for antinuclear antibody, and normal 24-hour urinary oxalate level (18 mg in 24 hours) whereas serum was intact parathormone (PTH) was elevated at 93 pg/ml, and serum phosphate level was reduced to 2 mg/dl.

The child was advised salt-restricted diet and started on enalapril at 0.4 mg/kg/day gradually escalated to 0.6 mg/kg/day and later candesartan was added @ 0.2 mg/kg/day to combat the proteinuria. Suspecting nephritonephritic pathology, light microscopy, and immunofluorescent study were done which was non-yielding except for some RBC tubular casts which ruled out the glomerular causes of haematuria. However, electron microscopy showed mild effacement of foot processes of a visceral epithelial cell as well a few glomerular capillaries showed variation in glomerular basement membrane collagen including the formation of electron-lucent intramembranous zones (Figure 2).

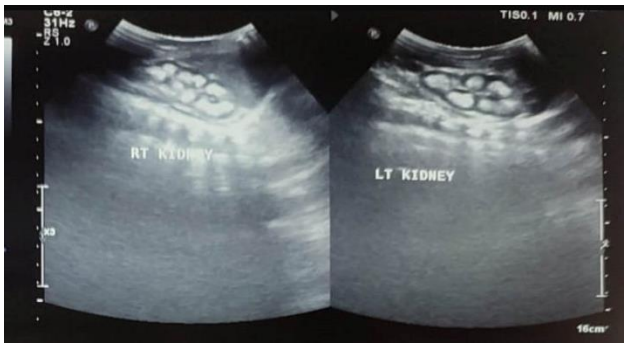

Figure 1: Supplemental figure depicts the ultrasound images showing nephrocalcinosis.

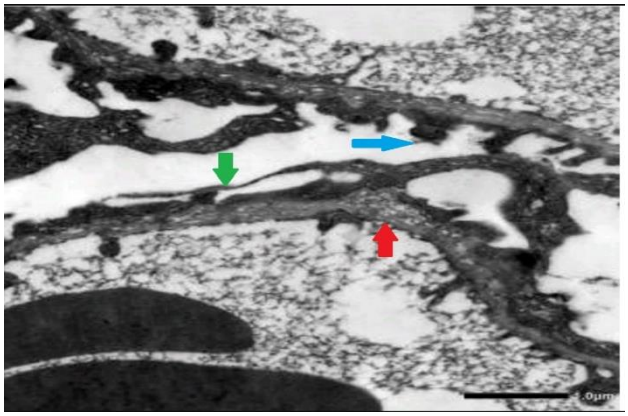

Figure 2: The supplemental figure shows kidney biopsy specimen under electron microscopy glomerular basement membrane thickening (indicated by red arrow) and effacement of foot processes (indicated by green arrow) in comparison to normal foot processes (indicated by blue arrow).

To derive further correlation with type IV collagen abnormalities, brainstem evoked audiometry (BERA) was performed which was non-yielding. Also, no signs of lenticonus/keratoconus were found on slit lamp examination. Whole exome sequencing further validated Alport's syndrome type 1 suggesting the occurrence of a pathogenic variantc.1892dup (p.Gly632ArgfsTer2) causing mutation in COL4A5(+) located in EXON 25 showing X-linked dominant inheritance. Parental testing could not be performed due to financial constraints.

DISCUSSION

Arthur C Alport first described a hereditary congenital haemorrhagic nephritis consisting of a classical triad of nephropathy, deafness, and hearing which posthumously was renamed Alport syndrome. The prevalence of this disease ranges from 1:5000 to 1:53000 and the most common pattern of inheritance is X linked followed by autosomal recessive and the defect primarily involves COL4A3, COL4A4, and COL4A5 genes.[4] Collagen type IV is fundamentally composed of six different α units which assemble themselves into three unique tissue-specificheterotrimers (α1α1α2, α3α4α5, and α5α5α6) which are indispensable for structural integrity and functional maturation of GBM. In Alport syndrome, the defect lies in the congregation of α3α4α5 heterotrimer, resulting in pathogenic instability of the basement membrane.[5]

Children with Alport syndrometypically present with a myriad of nephrogenic symptoms in the form of mild intermittent gross and microscopic haematuria and low-grade proteinuria classically detected in their first decade of life. If left untreated patients may progress to severe proteinuria and end-stage renal disease (ESRD) and the median age of presentation of ESRD is 7–39 years.[5] In addition to renal manifestations, the disease is phenotypically associated with sensorineural deafness and a plethora of ophthalmological symptoms. Early identification of ocular manifestations is important as in approximately 40% of patients these symptoms precede proteinuria.[5] Among ocular presentations dot and flake retinopathy is seen in 80% of patients which is a poor prognostic indicator however more pathognomic findings are anterior lenticonus (seen in 25% cases) and posterior polymorphous corneal dystrophy.[5] Other rare findings include microcornea, keratoconus, bull's eye maculopathy, iris atrophy, cataracts, spontaneous lens rupture, and retinal pigmentation. In our case, there was no detectable ocular pathology. In almost 80% of patients, high-tone sensorineural deafness is associated which usually manifests at primary school-going age or within the second decade and this explains the non-detection of sensorineural hearing loss in our case.[3,5]

Atypical associations such as gastroesophageal leiomyomatosis, mitral valve prolapse, ventricular septal defect, and ruptured intracranial aneurysm have been reported with childhood Alport syndrome to date.[6] Here in we present a novel association of medullary nephrocalcinosis which is the first such to be reported worldwide. Nephrocalcinosis itself is a rare phenomenon that is defined as the calcification of renal parenchyma which is broadly classified into cortical, medullary, cortical and medullary partially combined nephrocalcinosis whereas medullary nephrocalcinosis is the most common variety but never found to be associated with Alport syndrome.[7,8] However, Alport syndrome has been documented as a cause of cortical nephrocalcinosis in medical literature and has also been reported in a 47-year-old male patient by Schephens et al who had extensive form of renal damage.[7] Herein we present the unusual coalition of medullary nephrocalcinosis detected by ultrasonographyprobably caused by underlying secondary hyperparathyroidism as evidenced by lab parameters in the form of hypercalcaemic normocalcuria, high parathormone and vitamin D levels with hypophosphatemia as other causes like diuretic abuse, hyperuricemia, thyroid dysfunction, hyperoxaluria, sickle cell anaemia, renal tubular acidosis were ruled out.

The treatment recommendation regarding the use of angiotensin-converting enzyme inhibitors (ACEI) is extrapolated from the ESCAPE trial in children with chronic kidney disease and the EARLY PROTECT trial in children with Alport syndrome. In our case, the patient was initially started on Enalapril @ 0.4 mg/kg/day to combat proteinuria and hypertension. It has also been inferred that in patients having urine protein-creatinine ratio of more than 1.0 an angiotensin receptor blocker or an aldosterone antagonist can be added if there is poor control of proteinuria despite optimum dosing of acetyl choline esterase inhibitors (ACEI) and this additional therapy has substantially decreased the proteinuria in some studies. Hence in our case, candesartan was also added to enalapril. The patient is under strict follow-up for control of hypertension and proteinuria along with routine annual audiological and ophthalmological evaluation. Renal transplantation in Alports syndrome has a favourable outcome and may be a future requirement in case the disease deteriorates. As a recent breakthrough, urinary epidermal growth factor (uEGF) has been proven to be an important prognostication tool in childhood alports syndrome.[9,10]

CONCLUSION

Alport syndrome is a progressive hereditary nephropathy which has been highlighted here due to its novel genotypic variant and unusual association with medullary nephrocalcinosis not reported previously in medical literatures and also focuses on curbing disease progression more effectively.

Recommendations

This is a case report of childhood Alport syndrome of X-linked dominant inheritance which is associated with an

atypical association of medullary nephrocalcinosis first such to be reported worldwide.

This case also adds the use of angiotensin receptor blockers in conjunction with ACEIs to combat persistent proteinuria more effectively.

Adds another novel variant to the recently evolving genetic enigma of Alport's syndrome.

ACKNOWLEDGEMENTS

Authors would like to thank the contributors who helped from managing the patient primarily and designing the manuscript. They also acknowledge the full cooperation from the guardian of the patient.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Tryggvason K, Zhou J, Hostikka SL, Shows TB. Molecular genetics of Alport syndrome. Kidney Int. 1993;43(1):38-44.
2. Miner JH. Pathology vs. molecular genetics:(re) defining the spectrum of Alport syndrome. Kidney Int. 2014;86(6):1081-3.
3. Colville DJ, Savige J. Alport syndrome. A review of the ocular manifestations. Ophthalmic Genet. 1997;18:161-73.
4. Gibson J, Fieldhouse R, Chan MM, Sadeghi-Alavijeh O, Burnett L, Izzi V, et al. Prevalence estimates of predicted pathogenic COL4A3–COL4A5 variants in a population sequencing database and their implications for Alport syndrome. J Am Soc Nephrol. 2021;32(9):2273-90.
5. Kruegel J, Rubel D, Gross O. Alport syndrome—insights from basic and clinical research. Nature Rev Nephrol. 2013;9(3):170-8.
6. Kugelman A, Grief Y, Gerhoni-Baruch R, Berkowitz D, Best LA, Guralnik L, Bentur L. Pulmonary presentation of esophagealleiomyomatosis associated with Alport syndrome in childhood. Isr Med Assoc J. 2003;5(4):293-4.
7. Schepens D, Verswijvel G, Kuypers D, Vanrenterghem Y. Renal cortical nephrocalcinosis. Nephrology Dialysis Transplantation. 2000 Jul 1;15(7):1080-2.
8. WHO. What is nephrocalcinosis?, 2019. Available at: https://healthjade.net/nephrocalcinosis/#googtte. Accessed on 10 November 2023.
9. 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.
10. Kashtan CE, 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 Nephrol. 2013;28:5-11.

Cite this article as: Pradhan P, Kapat A, Mandal AK, Bala AK. An unusual coalition of medullary nephrocalcinosis with a novel genotypic variant of Alport syndrome type-1. Int J Res Med Sci 2023;11:4531-4.