NEPHROTIC SYNDROME IN A CHILD WITH ALPORT SYNDROME: A CASE REPORT

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ABSTRACT

Alport syndrome is a disorder affecting basement membranes in the glomeruli, cochlea, and eyes due to mutations in collagen IV genes (COL4A3, COL4A4, COL4A5). It exhibits genetic and phenotypic variability and can be inherited via X-linked, autosomal recessive, or autosomal dominant patterns. Those with Alport syndrome face a considerable risk of kidney failure along with potential sensorineural hearing loss and eye abnormalities. Early diagnosis is vital due to the availability of effective interventions for kidney disease related to Alport syndrome. We are presenting a case report of a patient, 08 years old boy who presented with nephrotic syndrome and was ultimately diagnosed with a case of chronic kidney disease due to Alport syndrome. Early diagnosis of Alport syndrome can be challenging because of the disorder's genotypic and phenotypic complexity. Regular follow-up and vigilant monitoring, along with clinical examination and workup, can lead to an exact diagnosis.

KEYWORDS: *Alport Syndrome, Collagen Type IV Genes, COL4A5, X-Linked, Sensorineural Hearing Loss, Nephrotic Syndrome*

INTRODUCTION

Alport syndrome or hereditary nephritis is a genetically heterogeneous disease caused by mutations in the genes coding for collagen type IV, which is a major component of the basement membrane.[1] Approximately 85% has x-linked inheritance, whereas 15% has autosomal recessive pattern. Due to these variable genetic alternations it is associated with marked variability in natural history, histopathological findings, and clinical presentation such as hematuria, proteinuria leading to renal failure, and extra renal manifestation of visual and hearing impairment.[2,3] Alport syndrome can be challenging to diagnose, especially in the pediatric population, due to variable and overlapping symptoms. It can be misdiagnosed as another renal disorder. Around 7%[4] of cases present as proteinuria and are misdiagnosed as simple nephrotic syndrome or steroid-resistant. We are presenting a case report of 08 years old boy who was initially managed as steroid-sensitive nephrotic syndrome and then as a late non-responder, steroid-resistant nephrotic syndrome. Later, he was finally diagnosed as case of Alport syndrome with chronic kidney disease.

CASE PRESENTATION

Patient 08 years old boy was diagnosed and managed as a case of steroid-sensitive nephrotic syndrome six years back in 2019. On initial presentation, the chief complaint was chief compliant of body swelling and proteinuria. Initially, he was treated for nephrotic syndrome and responded well to steroids. The patient is a product of consanguineous marriage. He got treatment at another center. He had multiple relapses during the course of treatment in the first year of management. Later on, he showed resistance to steroids after one year in 2020. He was managed as a case of steroid-resistant nephrotic syndrome, a late non-responder, and started on tacrolimus. His first biopsy was done, which was suggestive of mesangioproliferative glomerulonephritis with immunofluorescence showing nonspecific deposits in 2020. The patient was given tacrolimus for 1.5 year and he responded well to treatment. Patient remained symptom-free for 1.5 years after stopping all treatment. He again presented with feature of nephrotic syndrome and also got progressive hearing loss in December 2023. Alport syndrome was also considered in the differential diagnosis. The patient was again started on oral steroids and tacrolimus. There was no response to immunosuppressive therapy for 12 weeks. Because of poor response to medicines, his biopsy was repeated in April 2024, which was suggestive of focal segmental glomerulonephritis, and immunofluorescence was negative. As there is no electron microscopy available in Pakistan, the definite diagnosis of Alport syndrome was not possible on histopathology. The hearing loss patient followed up with Audiology, and he was advised for hearing aid. His eye examination was done to rule out anterior lenticonus, and it was normal,

keeping Alport syndrome in the differential diagnosis. There is no family history of any renal disease. Regular follow-up has been done. Despite treatment, the patient showed a rising trend in renal function tests, including urea and creatinine. The patient was not responding well to management, leading to progression to stage IV chronic kidney disease. Parents were counselled regarding a renal transplant. Instead of a renal transplant, keeping FSGS as the primary pathology, when whole exome sequencing (WES) was done, it showed COL4A5 gene mutation (heterozygous), and the patient turned out to be an Alport syndrome with chronic kidney disease. Family screening of the COL4A5 c.81+1G>C variant showed the mother is a heterozygote. Other heterozygous variants were identified in the ALG6, ZNF142, and NEMF genes. The patient is now on regular follow-up with renal replacement therapy. At every step of management, parents were counseled about the patient's condition, management, treatment plan, outcome, and prognosis. Proper consent from parents was taken for this case report.

DISCUSSION

Alport syndrome is a hereditary kidney disease with different inheritance patterns. Mutations in genes COL4A3, COL4A4, and COL4A5 (encoding collagen IV chains) cause AS. It affects about 1 in 5,000 to 1 in 10,000 people. It accounts for 0.5% of new kidney failure cases in adults.[1,2] Three classical hereditary mendelian patterns of inheritance exist, including X-linked, autosomal dominant, and recessive, amongst which X-linked is the most common (85%).[5] Our case report shows an X-linked pattern with COL4A5 mutation, and this mutation disrupts the structure and function of the basement membrane, leading to different clinical manifestations.[6] COL4A5 -related disorder is inherited in an X-linked manner, and the same hemizygous variant was detected in the patient's mother. Since there is a possibility of mild symptoms due to X inactivation pattern in women, clinical evaluation of the mother was done, and it was normal. There is a 50% risk for her to pass on this variant to her offspring. Genetic counseling of parents was done in extreme detail. Alport Syndrome has an insidious onset, and many cases are being misdiagnosed or underdiagnosed, solely based on clinical manifestations.[7] Alport syndrome can be diagnosed in patients with persistent glomerular hematuria (with or without proteinuria) if they meet any of these criteria: 1) Abnormal type IV collagen staining: In glomerular or cutaneous basement membranes. 2) Characteristic electron microscopy findings: Tearing/delamination of glomerular basement membrane. 3) Pathogenic mutations: In COL4A5 (one mutation) or COL4A3/COL4A4 (two mutations). But in our case, the patient's initial presentation in 2019 was typical of nephrotic syndrome. Interestingly patient responded well to oral steroids and was managed as a case of steroid-sensitive nephrotic syndrome. As the patient had multiple relapses, and later on the patient showed no response to oral steroids then patient was started on tacrolimus, and a renal biopsy was done. Histopathology was initially suggestive of mesangioproliferative glomerulonephritis. There was a complete response to tacrolimus, and the patient also remain symptom free for 1.5 years. Only when the patient relapsed after 1.5 year and there was no response to oral steroids and tacrolimus, a repeat biopsy was planned, keeping progressive hearing loss in lieu. Due to the lack of facility of electron microscopes in Pakistan, only light microscopy and immunofluorescence were done, and it showed FSGS. The patient was showing progressive derangement in renal function tests, and a renal transplant was planned. It is necessary to do gene analysis for a definite diagnosis because Alport Syndrome was also in the differential diagnosis, which has unusual onsets and manifestations. In one case study by Zhuo Deng et al., [1], the clinical presentation was similar to nephrotic syndrome, like our case report. In the literature 9.1%[4] of patients with Alport syndrome presented with proteinuria, but these patients are steroid resistant; our patient was initially steroid sensitive. Changes in the glomerular basement membrane (GBM) and abnormal interactions between stromal cells and podocytes result in secondary pathological changes causing proteinuria and the development of focal segmental glomerulosclerosis (FSGS) lesions. These changes explain the significant proteinuria and FSGS lesions seen under light microscopy.[8] This explains the biopsy finding of our case, which leads to misdiagnosis. Furthermore, it has been observed that the extra-renal manifestation of Alport syndrome is usually late-onset, which makes it even more difficult to diagnose in earlier age.[8] In the paediatric population, especially in early ages, it is very difficult to diagnose Alport syndrome. Due to the lack of typical clinical manifestations in the early stage, such as auditory or visual abnormalities, Alport syndrome (AS) in children may be misdiagnosed as other renal disorders like IgA nephropathy, minimal change disease, nephritic, or nephrotic syndrome.[9] Pathology and genetic testing provide reliable confirmation of the diagnosis. In clinical practice, especially in third one country like ours, renal pathological and genetic examinations are advisable for patients with nephropathy unresponsive to steroid therapy for early diagnosis and management of children. For patients diagnosed with AS, devotion to

treatment guidelines for appropriate drug therapy is recommended to reduce proteinuria, slow renal progression, and enhance survival. Additionally, early kidney transplantation is advocated for patients with AS progressing to chronic kidney failure.

CONCLUSIONS

Though nephrotic syndrome is common in the paediatric population, Alport syndrome should be considered in cases with steroid resistance (late responder), poor response to immunosuppression, and extra-renal features such as hearing lo**ss**. In a resource-limited setup where electron microscopy is unavailable, genetic testing is essential for diagnosis. Early identification of a COL4A5 mutation helps avoid unnecessary immunosuppression and guides appropriate counseling and transplant planning.

CONFLICT OF INTEREST: None

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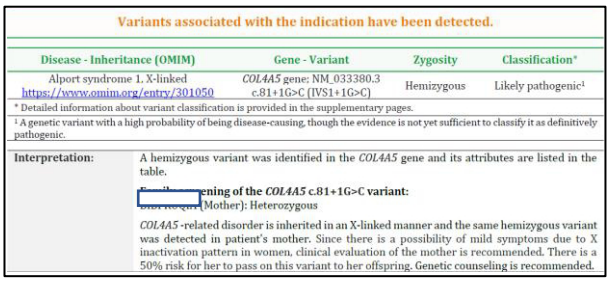
Patient Picture with Alport Syndrome and Chronic Kidney Disease:



Variants associated with the indication have been detected.

Disease - Inheritance (OMIM)	Gene - Variant	Zygosity	Classification*
Alport syndrome 1, X-linked https://www.omim.org/entry/301050	*COL4A5* gene; NM_033380.3 c.81+1G>C (IVS1+1G>C)	Hemizygous	Likely pathogenic[1]

* Detailed information about variant classification is provided in the supplementary pages.

[1] A genetic variant with a high probability of being disease-causing, though the evidence is not yet sufficient to classify it as definitively pathogenic.

Interpretation: A hemizygous variant was identified in the *COL4A5* gene and its attributes are listed in the table.

[redacted]ening of the *COL4A5* c.81+1G>C variant:

[redacted] (Mother): Heterozygous

COL4A5 -related disorder is inherited in an X-linked manner and the same hemizygous variant was detected in patient's mother. Since there is a possibility of mild symptoms due to X inactivation pattern in women, clinical evaluation of the mother is recommended. There is a 50% risk for her to pass on this variant to her offspring. Genetic counseling is recommended.

Whole exome sequencing (WES) report

AUTHORS CONTRIBUTION

Syed Sajid Hussain Shah - *Concept & Design; Data Acquisition; Data Analysis/Interpretation; Drafting Manuscript; Critical Revision; Supervision; Final Approval*
Munaza Naeem - *Concept & Design; Data Acquisition; Drafting Manuscript; Final Approval*

The authors accept responsibility for all aspects of the work and will ensure that any concerns regarding the accuracy or integrity of any part are properly investigated and resolved.