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Unusual Presentation of Alport Syndrome in a Female Patient without Hematuria with affected all Male Offspring: A Rare Case Report

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Abstract

Alport syndrome (AS) is an inherited disorder mainly involves basement membrane clinically characterized by hematuria, deafness and visual abnormalities. Males are mostly affected. Here we present a case of 40 years old female who has family history of renal impairment, hypertension, hearing loss presented with nephrotic range proteinuria and renal impairment. After evaluation she was subsequently diagnosed as a case of Alport syndrome with ESRD.

Introduction

Alport syndrome was first described by a British physician named Cecil Alport in 1927 [1,2]. This inherited disease affects 1 in 5000 live births, primarily involving male children [2]. This rare glomerulopathy accounts for 3% of chronic kidney disease (CKD) in children and 0.2% of end-stage renal disease (ESRD) in adults [3]. The primary pathology lies in the glomerular basement membrane due to a mutation in the COL4A5 gene, responsible for the formation of the alpha-5 chain of type IV collagen fibers [4]. Six isoforms of type IV collagen—α1(IV)–α6(IV)—encoded by six genes (COL4A1–COL4A6) are variably expressed in basement membranes. These type IV collagen chains self-assemble to form specific triple helices, which then create a tertiary network with laminin, entactin/nidogen, and proteoglycans to form the basement membranes. The α3-α4-α5(IV) network is the predominant type IV collagen network in the mature glomerular basement membrane (GBM) and in certain basement membranes of the cochlea and eye [5]. Mutations in the α3, α4, or α5 chains of type IV collagen lead to the loss or disruption of the α3-α4-α5(IV) network, dysfunction of affected basement membranes, and the clinical manifestations of Alport syndrome [6]. Alport syndrome is genetically heterogeneous, inherited in an X-linked (85%), autosomal recessive (15%), or autosomal dominant (5%) pattern [7]. The principal clinical manifestations include persistent hematuria, progressive renal failure, high-frequency sensorineural deafness, and visual impairments. Isolated proteinuria is a less common manifestation [8]. Furthermore, females are believed to have less severe renal involvement in Alport syndrome [2]. Here, we present a case of female Alport syndrome with both proteinuria and severe renal involvement but no hematuria.

Case History

A 40-year-old female homemaker from a lower-middle-class family was admitted to our hospital with complaints of swelling in both of her legs for the past one and a half months. Initially, there was facial puffiness, which later involved both legs. She also noticed progressive pallor, weakness, anorexia,

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nausea, and occasional vomiting. Her urine output was normal. The urine was frothy but never associated with hematuria. She mentioned she has been suffering from hypertension for the past 10 years, which was initially controlled with medication; however, she progressively had to increase her antihypertensive dose. Additionally, she reported progressive hearing loss, which has been worsening over time.

A detailed family history revealed that she is the third child of non-consanguineous parents. Her youngest brother was diagnosed with hypertension and ESRD at the age of 12 years. He presented with hematuria and proteinuria, as well as hearing difficulties, but no visual impairment. Unfortunately, he passed away after his diagnosis due to sepsis. The patient had a non-consanguineous marriage and has three sons. Her firstborn son had hearing difficulties since the age of seven and required hearing aids for deafness. At the age of 17, he was diagnosed with ESRD, and despite undergoing hemodialysis for three months, he unfortunately passed away. At that time, the patient and her second and third sons underwent screening investigations, revealing that they were all suffering from similar conditions, including hearing difficulties, proteinuria, hypertension, and renal impairment. In her mid-thirties, the patient herself was diagnosed with proteinuria, renal impairment, and hypertension. Additionally, her third son, at only three years old, had hematuria. Since then, they have all been on conservative management. Her second son developed ESRD at the age of 18 and is currently on maintenance hemodialysis (Figure 1). The patient also has some visual impairment (Table 1).

On examination, the patient appeared edematous and anemic, with a pulse of 80 beats per minute and a blood pressure of 150/80 mmHg (on medication) (Figure 2). The heart sounds (S1 and S2) were normal, and her lungs were clear. Weber and Rinne tests revealed sensorineural deafness (Table 2). Her visual acuity was 6/9 in the right eye and 6/12 in the left eye. Fundoscopic examination revealed grade 3 hypertensive retinopathy.

A provisional diagnosis of Alport syndrome was made on the basis of clinical examination, family history, investigations of the patient and genetic analysis of her younger son. She was counselled regarding the outcome of diseases, treatment modalities like conservative management, dialysis, renal transplant. Patients choose conservative therapy. She was advised for regular follow up.

Table 1: Laboratory and Radiological Investigations.

Investigations	Findings
CBC	Hb 7.6 gm/dl, WBC: 9000/l, PLT: 200000, ESR: 40mm in 1st hour
Urine R/E (on repeated test)	Protein 3+, no RBC, Cast nil
UTP	4.8 gm/day
S creatinine	8.1 mg/dl
S Electrolytes	Sodium 136, potassium: 5.2, chloride: 99 mmol/L
S albumin	3.6 gm/dl
S calcium	8.6 mg/dl
S Phosphate	6.6 mg/dl
S uric acid	10.2 mg/dl
S PTH	663 pg/ml
RBS	4.3 mmol/L
ANA	Negative
USG of whole abdomen	Right kidney: 9.2 cm, Left kidney: 9.3 cm Cortical echogenicity is increased.CMD is reduced.
Pure tone audiometry	Right ear: mild to moderate sensorineural hearing loss Left ear: moderate sensorineural hearing loss

Table 2: Renal biopsy & genetic analysis of 3rd son of the patient.

Renal biopsy	**Light microscopic features**: matrix increased, GBM focally thick. **DIF**: There was deposition of IgG:2+, IgA: 2+, C3: 3+**Electron microscopy**: not done.
Genetic analysis	Mutation in the COL4A5 gene associated with Alport Syndrome

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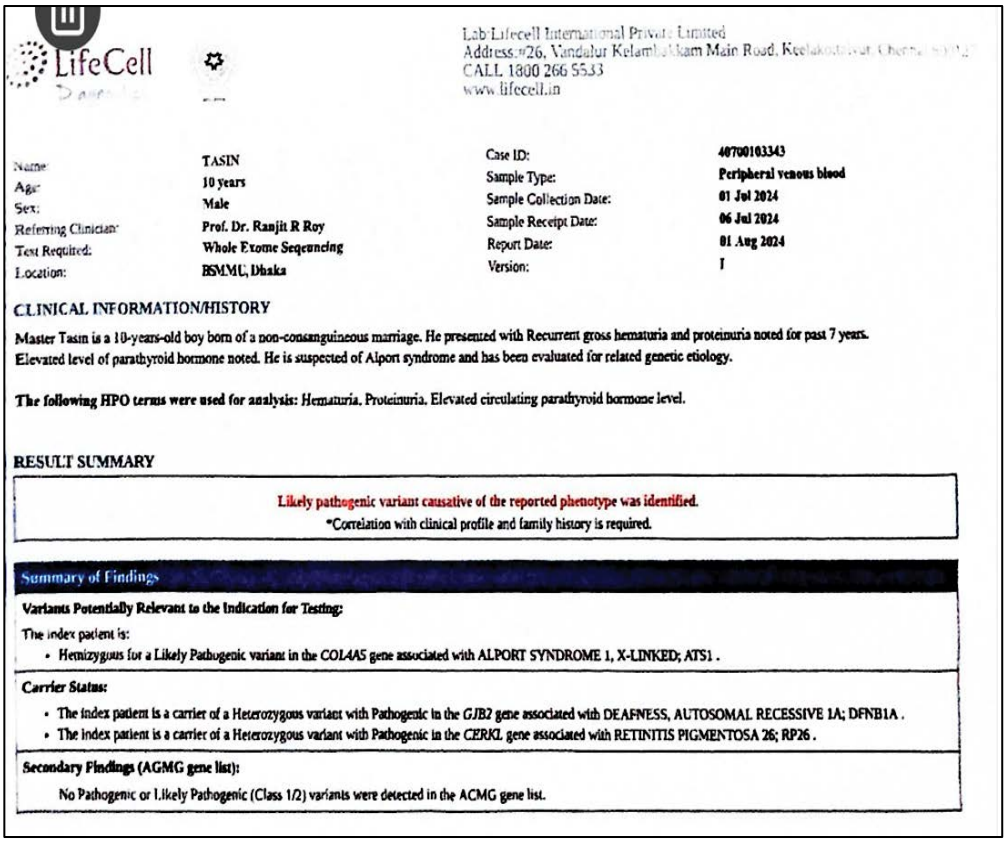

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Name:	TASIN	Case ID:	40700103343
Age:	10 years	Sample Type:	Peripheral venous blood
Sex:	Male	Sample Collection Date:	01 Jul 2024
Referring Clinician:	Prof. Dr. Ranjit R Roy	Sample Receipt Date:	06 Jul 2024
Test Required:	Whole Exome Sequencing	Report Date:	01 Aug 2024
Location:	BSMMU, Dhaka	Version:	1

CLINICAL INFORMATION/HISTORY

Master Tasin is a 10-years-old boy born of a non-consanguineous marriage. He presented with Recurrent gross hematuria and proteinuria noted for past 7 years. Elevated level of parathyroid hormone noted. He is suspected of Alport syndrome and has been evaluated for related genetic etiology.

The following HPO terms were used for analysis: Hematuria, Proteinuria, Elevated circulating parathyroid hormone level.

RESULT SUMMARY

Likely pathogenic variant causative of the reported phenotype was identified.
*Correlation with clinical profile and family history is required.

Summary of Findings

Variants Potentially Relevant to the Indication for Testing:

The index patient is:

- Hemizygous for a Likely Pathogenic variant in the *COL4A5* gene associated with ALPORT SYNDROME 1, X-LINKED; ATS1 .

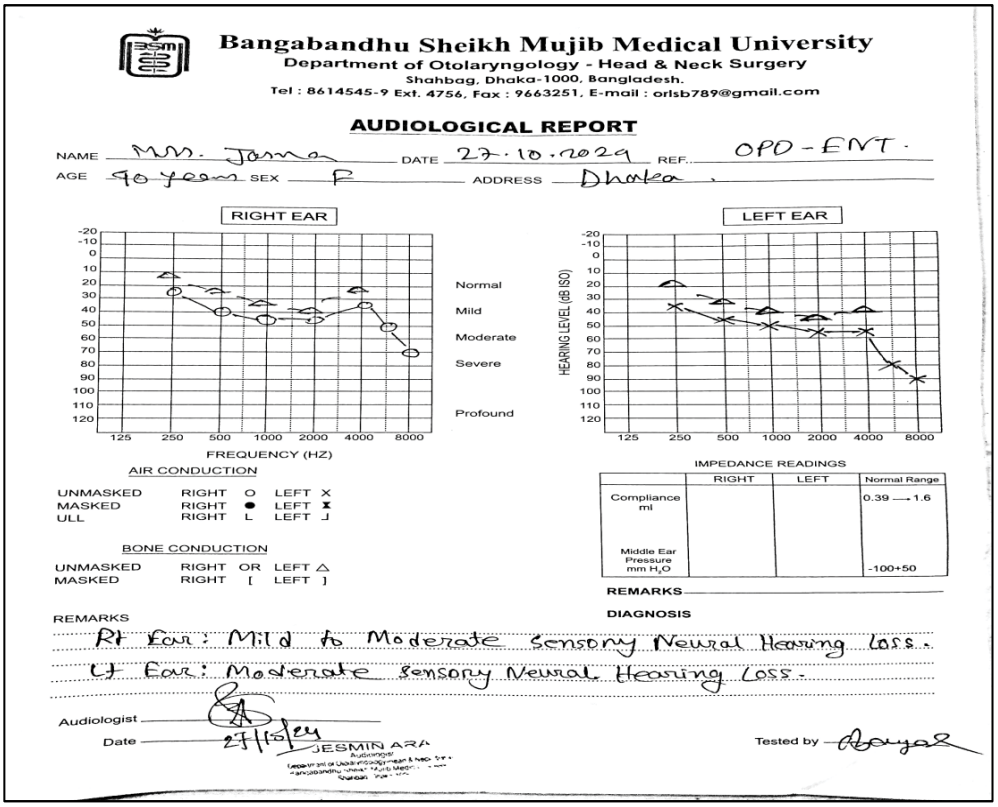
Carrier Status:

- The index patient is a carrier of a Heterozygous variant with Pathogenic in the *GJB2* gene associated with DEAFNESS, AUTOSOMAL RECESSIVE 1A; DFNB1A .
- The index patient is a carrier of a Heterozygous variant with Pathogenic in the *CERKL* gene associated with RETINITIS PIGMENTOSA 26; RP26 .

Secondary Findings (AGMG gene list):

No Pathogenic or Likely Pathogenic (Class 1/2) variants were detected in the ACMG gene list.

Figure 1: Genetic exome test (Whole exome sequencing test).



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AUDIOLOGICAL REPORT

NAME Mst. Jorna DATE 27.10.2024 REF. OPD - ENT.
AGE 40 years SEX F ADDRESS Dhaka.

RIGHT EAR

Normal
Mild
Moderate
Severe
Profound

LEFT EAR

AIR CONDUCTION

UNMASKED	RIGHT O	LEFT X
MASKED	RIGHT ●	LEFT ⧗
ULL	RIGHT L	LEFT ⌋

BONE CONDUCTION

UNMASKED	RIGHT OR	LEFT △
MASKED	RIGHT [	LEFT]

IMPEDANCE READINGS

	RIGHT	LEFT	Normal Range
Compliance ml			0.39 → 1.6
Middle Ear Pressure mm H_2O			-100+50

REMARKS

DIAGNOSIS

REMARKS
Rt Ear: Mild to Moderate Sensory Neural Hearing Loss.
Lt Ear: Moderate Sensory Neural Hearing Loss.

Audiologist
Date 27/10/24 JESMIN ARA Audiologist

Tested by Aayat

Figure 2: Pure tone audiometry.

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Discussion

For much of the 20th century, it was believed that affected females in families with Alport syndrome (AS) would follow a benign course. Alport himself supported this idea. In 1927, he wrote, “the females with Alport Syndrome have deafness and hematuria and live to old age” [2]. Even in the 1960s, physicians believed that “females usually remain well throughout life… and only rarely have women died of the disease” [9]. However, in the 1960s and 1970s, case reports of severely affected females with Alport syndrome began appearing in the literature [10]. In 1985, a report from Paris described the natural history of 36 women from 24 families with Alport syndrome [11]. One-quarter of heterozygous females progressed to ESRD before age 35, while another 14% reached end-stage renal disease (ESRD) after age 45. This cohort study identified predictors of progressive kidney disease, including gross hematuria in childhood, nephrotic syndrome, and diffuse glomerular basement membrane (GBM) thickening evidenced by electron microscopy. This study brought attention to the significant risk for ESRD progression in heterozygous females with AS.

A comprehensive natural history study of heterozygous females was conducted by the European Community Alport Syndrome Concerted Action Study, published in 2003 [12]. Among 349 heterozygous females from 195 families with confirmed COL4A5 mutations, comparisons were made to affected hemizygous males in the same families. Microscopic hematuria was observed in 95.5% of XLAS heterozygotes, and 75% of XLAS heterozygotes developed proteinuria. As with other renal diseases, the presence of proteinuria was a significant risk factor for ESRD progression ($p < 0.001$). In this study, nearly 90% of affected males developed ESRD by age 40, while only 12% of heterozygous females reached ESRD. After age 60, between 30–40% of heterozygotes developed ESRD. These findings confirmed a substantial burden of kidney disease in the female population, challenging the previously accepted "benign carrier" designation.

In affected males, there is a significant genotype–phenotype correlation [13], but such correlations are not observed in females [12]. Additionally, there is inconsistency in phenotype among females within the same family. Several studies suggest that differences in X-chromosome inactivation may influence disease severity in heterozygous females [14,15]. Although genetic testing could not be performed in our case report, the patient's son had genetically confirmed Alport syndrome, implying the patient likely has the same disease. The patient began experiencing proteinuria before age 35 and progressed to ESRD by age 40. Although she never had hematuria—a common manifestation of Alport syndrome—she exhibited significant proteinuria. Nephrotic-range proteinuria and sensorineural deafness are important risk factors for CKD progression.

The purpose of our case report is to highlight the importance of screening female family members in cases of hereditary nephritis to assess renal involvement, as females may be severely affected. While Alport syndrome is incurable, disease progression can be slowed by controlling hypertension and reducing proteinuria. ACE inhibitors and ARBs are beneficial options. Additionally, genetic counseling and psychological support are essential, as many mothers feel guilt about passing the disease to their children. Advanced treatments under investigation include paricalcitol, sodium-glucose co-transporter-2 inhibitors, bardoxolone methyl, anti-microRNA-21 oligonucleotides, recombinant human pentraxin-2, inhibitors targeting lysyl oxidase-like-2, hydroxypropyl-b-cyclodextrin, sodium 4-phenylbutyrate, and stem cell therapy [16]. Patients with AS are suitable candidates for renal transplantation, though there is a risk of developing antiglomerular basement membrane antibodies post-transplant, necessitating close monitoring.

Conclusion

Further studies are essential to gain a better understanding of Alport syndrome in females. Women with a family history of Alport syndrome should undergo comprehensive evaluations to rule out renal involvement. Early diagnosis can help slow disease progression if timely interventions are applied. Genetic counseling is crucial to reduce the risk of passing the condition to future generations. In developing countries like Bangladesh, steps should be taken to establish facilities for genetic testing and analysis.

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