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A FAMILY OF CHRONIC KIDNEY DISEASE – AN INTERESTING CASE REPORT

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ABSTRACT **Background:** Family history is increasingly being recognized as a useful tool for risk assessment of chronic kidney diseases. But most studies largely focused on some Mendelian disorders. Alport syndrome is one among these, affecting type IV collagen. **Case Report:** We present a case of 43 year old female patient diagnosed with End stage kidney disease, with a family history of Chronic kidney disease in three generations. Despite absence of typical clinical manifestations, genetic testing revealed a novel variant in the COL4A5 gene, confirming X linked Alport syndrome. The patient's son, also tested positive for the same variant and rapidly progressed to End stage kidney disease by second decade. **Conclusion:** This case highlights the importance of genetic analysis in young patients with Chronic kidney disease. The identification of a novel variant in COL4A5 gene expands our understanding of Alport syndrome's genetic architecture. Hence this case underscores the need for increased awareness and availability of genetic testing and counselling services for families affected by kidney disease.

KEYWORDS : Chronic kidney disease, Family, Genetics, Alport.

INTRODUCTION

There are accumulating evidences that Chronic Kidney Disease (CKD) has a familial predisposition and are associated with a higher risk of End Stage Kidney Disease (ESKD) [1].

The most common causes of CKD include hypertension, diabetes mellitus, glomerular disease and polycystic kidney disease. Though polycystic syndromes and Alport disease, have well established patterns of Mendelian inheritance, the genetic architecture of the more common causes of CKD is more complex[2].

In recent years, our understanding of genetic causes of CKD has expanded significantly, evolving from Sanger sequencing to next-generation sequencing, gene panel analysis is now widely used to test for specific genes in genetic kidney disease. This helps to understand the presentation, risks and management of these genetic kidney diseases to provide comprehensive care to those with genetic kidney disease.

Herein, we report a case of patient diagnosed with ESKD and with CKD-ESKD diagnosed in three generations of the index patient, with genetic test positive for Alport syndrome.

Case Report

A 43 year old lady, who was known to have chronic kidney disease (CKD) of 2 years duration, but neither evaluated nor on medications, presented to our outpatient clinic with pedal oedema, reduced urine output and uremic symptoms of vomiting, poor appetite and generalised fatigue of 1 month duration in the year 2014. No history of hematuria or joint pains.

She was born out of 3rd degree consanguineous marriage, as second in birth order. Her family history was significant with CKD- ESKD in mother, elder brother and younger sister diagnosed at 40 years, 35 years and 19 years of age respectively and all expired after one year vintage of Hemodialysis (Figure 1). Their kidneys were contracted in imaging at presentation, and urine microscopy was normal.

Her obstetric history was significant with history of hypertension in her antepartum period (from 3rd month gestation) in first and third pregnancy, but stopped medications immediate postpartum and lost to follow up. Her second pregnancy was uneventful and no history of miscarriages. She noticed headache and pedal oedema 2 years later and on evaluation, had high blood pressures recording with Creatinine of 2.5mg/dl., but refused further workup.

In our evaluation, high blood pressures noted and laboratory investigations showed Hemoglobin of 8g/dl, normocytic in smear, Creatinine of 7 mg/dl and ultrasound abdomen of bilateral contracted kidneys .She was placed on maintenance Hemodialysis and underwent deceased donor renal transplant three years later, in the year 2017. Though there was delayed graft function with biopsy suggestive of antibody mediated rejection, for which she was subjected to six sessions of plasmapheresis and immunoglobulin and was discharged with creatinine of 0.8mg/dl on postoperative day 21.. Since then, patient has stable graft function with triple immunosuppresssion of Prednisolone, Tacrolimus and Myco-phenolate and regular follow up with us.

In the year 2022, her second son, 21 years old presented with anasarca with Hypertension and Creatinine of 1.7mg/dl and 24hour urine protein of 5g. No active sediments in urine. He underwent renal biopsy and Light Microscopy was suggestive of Focal segmental glomerulosclerosis(Not otherwise specified type) , and hence started on steroids, but subsequently his Electron microscopy turned out to be Alport syndrome (Figure 2).

Hence genetic analysis was done, which revealed a novel variant, c1807G>C (p.Gly603Arg), exon 25, in COL4A5 gene, with Hemizygous inheritance, suggestive of X linked Alport syndrome-1. He was on ACE inhibitors and conservative management. There was no hematuria or any ocular or hearing abnormalities. But his renal function deteriorated rapidly over the span of 1.5 years, being dialysis dependent in 2023.and currently on thrice weekly maintanence Hemodialysis. His siblings are asymptomatic with normal urine and renal function reports.

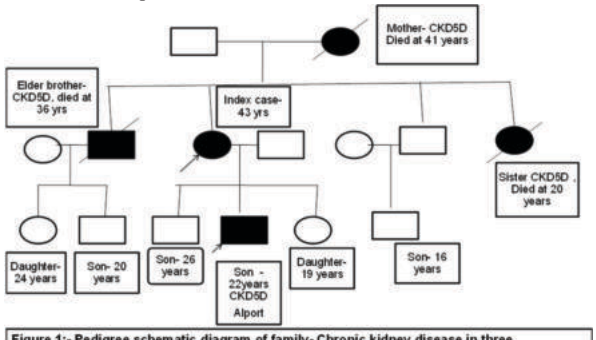

Figure 1:- Pedigree schematic diagram of family- Chronic kidney disease in three generations . .The patient described in this article is denoted by an arrow. Men are shown as squares and women as circles. Fully black denotes family members with end- stage kidney disease requiring kidney replacement therapy. Diagonal lines indicate deceased family members.

Figure 1: Pedigree of Family.

In view of renal disease in three generations, our index patient

underwent genetic testing and revealed same variant with Heterozygous inheritance, indicating X linked dominant Alport. Neither the index patient nor her mother, brother, sister had microscopic hematuria, ocular or hearing abnormalities.

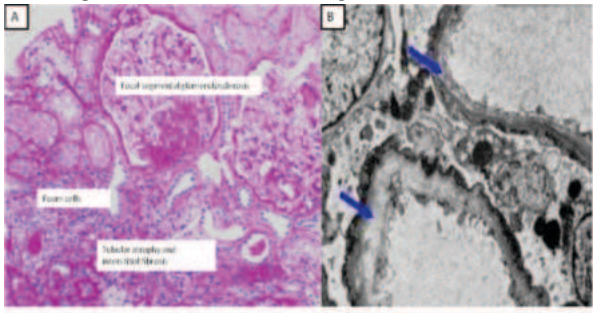

Figure 2- A- Light microscopy –PAS stain- showing focal segmental glomerulosclerosis, interstitial foam cells and interstitial fibrosis and tubular atrophy.
B- Electron microscopy- thickened and thinned glomerular basement membrane- Basket weave pattern.

Figure 2: Histopathology

DISCUSSION

Alport syndrome is a disease of type IV collagen (COL), with prevalence between 1 in 5000 and 1 in 53,000 individuals [3]. Type IV collagen is made of 6 genetically distinct alpha (α) chains arranged into three triple helical protomers (α1.1,2, α3.4.5 and α5.5.6) and mutations of Alport syndrome occur in the COL4A3, COL4A4 and COL4A5 genes which code for the α3, α4 and α5 chains, respectively, which would normally form the glomerular basement membrane[4].

X-linked Alport syndrome (COL4A5) makes up 80% of cases with autosomal recessive or autosomal dominant inheritance (COL4A3 and/or COL4A4) constituting about 15% and 5% of these cases, respectively. COL4A5 gene contains 51 exons and 50 introns, encoding 1685 amino-acids of type IV collagen α 5 chain in glomerular basement membrane [5].More than 900 different variants in COL4A5 have been identified so far, with missense mutation forming 43.6% [6].

It is reported that 50% of patients reach End Stage Kidney Disease (ESKD) by age 30 and have 50% renal survival rate of 32 years and in some both hearing loss and ESKD occur after age of 50 [7].The present case report followed a X linked dominant inheritance pattern, affecting three generations and both genders. However, due to lyonization in females, and variation in inactivation of X and based on inheritance of the same, the disease showed variable expression. Hence both male and female developed disease and landed in ESKD in second, third and fourth decade.

The present case report has identified a novel variant in COL4A5, which was not previously reported, and was present in both index patient and son. The mutation in exon 25, at 1807, from Guanine to Cytosine, resulted in change from Glycine, a neutral amino-acid to Arginine, which is basic. This change prevented the network formation of collagen trimers(α 3 α 4 α 5) and led to abnormal basement structure thus destroying filtration barrier and leakage of red cell and albumin causing loss of kidney function and finally, kidney failure. But the exact mechanism needs to be further elucidated.

Available literature revealed that the family history of kidney disease may be useful to identify individuals at high risk of Chronic Kidney Disease (CKD) early and accurately classify risk of ESKD. A nationwide population-based study of 1.76 million people in South Korea showed a strong familial aggregation of CKD such that those with an affected family member with CKD had a higher risk of incident CKD. In addition, once CKD had been diagnosed, family history of ESKD was also associated with a significantly higher risk of disease progression to ESRD [8]. Seaquist et al. found that there is a striking concordance of diabetic nephropathy between siblings with type 1 diabetes [9] and Lei et al. showed that the risk of ESKD was significantly higher in individuals with any family history of renal disease, and these associations could not be completely explained by clustering of other known risk factors for kidney disease within the family, such as diabetes and hypertension [10].

Several genome-wide association studies have identified many genetic regions associated with renal traits, such as diabetic nephropathy [11] and also the polymorphisms in the APOL1 (apolipoprotein L1) gene were found in 2010, which result in hypertensive nephrosclerosis and focal global glomerulosclerosis. The higher prevalence of pathogenic APOL1 allele in Black Americans are responsible for the higher burden of CKD in this population than in Whites [12]. Recently, Wu et al[13] and Zhang et al[14], conducted study in Taiwanese and European patients with ESKD, respectively and confirmed that the risk of CKD in individuals with an affected first-degree member was three times higher than that in the general population.

The utility of genetic testing is more than just making a correct diagnosis. A correct diagnosis with genetic disease may prevent unnecessary use of immunosuppressive drugs as in the presented case and may identify an optimal treatment in managing the disease. It also helps in estimating the risk of recurrence after receiving kidney transplantation. This is also being used in prenatal diagnosis. Patients and families should be provided with adequate information through genetic counselling. However the issues of affording genetic testing, availability of genetic counsellors and the expertise to interpret the results of genetic tests are not yet readily accessible in developing nations, thus forming a major hurdle.

CONCLUSION

We have reported a Family of Chronic Kidney Disease (CKD), with genetics suggestive of a new variant in X linked Alport syndrome, despite absence of typical clinical manifestations. So genetic testing has to be considered in young patients with family history even without typical clinical features, when light microscopy and immuno-fluorescence remains unclear.

As genetic causes of kidney disease are poorly understood the ongoing research of these, can potentially have a positive impact on the care of CKD population. This leads to a more patient centered approach of CKD management as well as to new treatment strategies.

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