ALPORT SYNDROME – A CASE REPORT ON APPROACH TO BASIC MANAGEMENT

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Abstract-
Alport syndrome is a rare genetic disorder which is characterized by progressive kidney disease and also cause abnormality of inner ear and eyes. It is also to be known as hereditary nephritis, hematuria, nephropathy, hereditary deafness and hemorrhagic familial nephritis.In healthy kidneys, nearly a million individual kidney subunits called nephrons, filter blood through a spherical sac called the glomerulus. The glomerulus consists of a membrane known as the glomerular basement membrane (GBM) that acts as a filtration barrier. Healthy individuals also have a substance called collagen of which there are several types which provides structural support to various tissues. Type IV Collagen exists as a heterotrimer: Three protein chains (α3, α3, and α3).

In Alport syndrome, mutations in the genes COL4A3, COL4A4, and COL4A5 in which each one is responsible for coding their respective protein chains cause a dysfunctional type IV collagen that compromises the ability of the GBM (Glomerular Basement Membrane) to act as a filtration barrier. As a result, the GBM becomes leaky and substances that should have retained in the body are lost including blood and proteins. The kidney tissue becomes permanently damaged and is replaced by fibrous tissue in a process called fibrosis.

Finally, the kidney becomes damaged due to kidney failure may cause patient to develop end stage renal disease or ESRD. It is important to note that Alport syndrome is a multisystem disease thereby it leads to hearing loss and ocular abnormalities [1, 2].

Keywords: **Alport syndrome, hematuria, GBM, and hemorrhagic familial nephritis.**

INTRODUCTION

Alport syndrome is a genetic disorder that is characterized by glomerulonephritis, that affects with hearing loss and eye abnormalities. It is caused by a genetic defect of type IV collagen which is usually inherited in an X-linked dominant pattern. In adolescence, patients initially develop more serious signs of chronic kidney disease (e.g., proteinuria) and may experience hearing loss or rarely vision problems.

In milder forms, patients may remain asymptomatic and only require monitoring. Diagnostic evaluation of Alport syndrome shows persistent hematuria on urinalysis and splitting of the glomerular basement membrane on kidney biopsy. The classic form usually leads to end-stage renal disease (ESRD) between the second and third decade of life and only definitive treatment is a kidney transplant.

It damages the tiny blood vessels in kidneys can leads to kidney disease and kidney failure. It can also cause hearing loss and problems within the eyes. Alport syndrome cause damage in kidneys by attacking the glomeruli. Glomeruli are the tiny filtering units inside kidneys [3, 4].

EPIDEMOLOGY

The reported incidence is approximately 1 in 50,000 newborns. It affects roughly 30,000 to 60,000 people in the US currently and 3% of children diagnosed with chronic kidney disease and 0.2% of adults who have ERSD with Alport syndrome. Rarely, the prevalence of Alport syndrome is not well-known although it is estimated to be 1 in every 50,000 live births worldwide while across Europe that estimate ranges from 1 in 100,000 people to 1 in every 11,000. Approximately 0.2 percent of all adults and 3 percent of all children in the U.S. with end-stage kidney disease have Alport syndrome, the U.S. Renal Data System (USRDS) reports [5, 6].

A study in 2,935 patients with chronic kidney disease in Australia published in theOrphanet Journal of Rare Diseases in 2014 identified that groups having Alport syndrome. From this data, researchers estimated the prevalence of Alport syndrome in general adult population was in Australia about 2.4 people out of every 1 million.About 85 percent of Alport syndrome cases are X-linked about 15 percent being autosomal recessive Alport syndrome (ARAS) and only a few cases of autosomal dominant Alport syndrome (ADAS) have been reported.

Women who carry the mutation causing XLAS may never show any symptoms of the disease, but have a 50 percent risk of passing the mutated gene to a child.Eye abnormalities are present in about 30 percent of all Alport cases [7, 8].

GENETIC TYPES OF ALPORT SYNDROME

There are three genetic types of Alport syndrome:

1. **X-linked Alport syndrome (XLAS)**: X-linked (related to the X chromosome) is the most common form of Alport Syndrome. About 80% of the people with this disease have the X-linked type. Without treatment, 90% of males develop kidney failure by 40 years old. Females develop kidney failure with less frequently and more slowly.
2. **Autosomal recessive Alport syndrome (ARAS)**: This is when both parents carry the abnormal gene and both parents pass the abnormal gene to the child. Both copies of the abnormal gene are needed to cause the autosomal recessive type of Alport Syndrome.
3. **Autosomal dominant Alport syndrome (ADAS)**: When one parent has the disease and passes the abnormal gene to the child one copy of the abnormal gene is needed to cause the disease.

Alport is a genetic disorder that can be passed down from parents in three different ways:

4. The first pattern of inheritance is called X-linked Alport syndrome (XLAS), in which the mutated gene is on the X-chromosome. Females have two copies of the X-chromosome, while males have a single copy, along with a Y-chromosome. Males typically show more severe symptoms, because females usually have an extra healthy X chromosome to mask the effect. 80% of all Alport cases are caused by this inheritance type. 50% of males require dialysis by age 25, and 90% develop ESRD by age 40.
5. The second pattern of inheritance is called autosomal recessive Alport syndrome (ARAS), in which the mutated gene is on a recessive autosome. 15% of all Alport cases are caused by this inheritance type. This disease has an early onset: kidney failure usually occurs by age 20. The second pattern of inheritance is called autosomal dominant Alport syndrome (ADAS), in which the mutated gene is on a dominant autosome. 5% of all Alport cases are caused by this inheritance type. This disease has a delayed onset: ERSD typically occurs in middle age [9. 10].

PATHOPHYSIOLOGY OF GENETICS AND THEIR INHERITANCE

Alport syndrome is a condition that develops due to mutations in three different genes – COL4A3, COL4A4 and COL4A5. The reason that the syndrome has a significant impact on the kidneys is because all of these genes provide instructions that affect the type IV collagen in a protein present in the kidneys.

This protein impacts the function of the glomeruli blood vessels in the kidneys which help with the filtering process. These capillaries remove water and waste from the blood to produce urine. When there are mutations in these genes, the kidneys do not carry out the filtering process as well as they should. This can result in chronic kidney disease (CKD) in the patient. This same collagen is also found in the inner ear structures. Abnormalities can result in hearing loss due to how they affect the function of the organ.This same collagen is also present in the eyes where keeping the shape of the lens. Mutations in the genes can result in a conical eye lens and flecks of discoloration in the retina [11, 12].

X-linked pattern of inheritance

In Alport syndrome, 80% of the cases are due to mutation in COL4A5, the X-linked pattern. For a male, this means that they have a mutation on their X chromosome but they do not have another X chromosome to compensate for this. The other chromosome is Y and is not affected.

Females have two X chromosomes, which means that even if they have the Alport Syndrome mutation on one chromosome, the other X chromosome can compensate. This can limit the development of symptoms for females in comparison to males [13, 14].

For males, this means that they can experience chronic kidney disease leading up to kidney failure and other more dramatic symptoms of the disease. In contrast, the impact on the females will be milder. Women tend to have hematuria (blood in the urine) but kidney problems are not as marked.

Additionally, males cannot pass on the X-chromosome to male offspring as male children receive the Y chromosome from their father. They can however pass their X chromosome to female offspring who will be a carrier for the syndrome [15].

Rare Types of Alport syndrome

The rare form of this syndrome is about 20% of cases in total. About 15% of these cases will have the autosomal recessive inheritance pattern. Patients will have mutations in the COL4A3 and COL4A4 genes. In autosomal recessive Alport syndrome men and women are both affected in similar ways. They will have symptoms such as renal failure, eye issues and haring defects.

A person with the condition would have to receive two mutations in the same genes from both parents. The carriers may show signs of blood in their urine (hematuria). Offspring of both sexes have 1 in 4 chance of inheriting the condition.

Another rare condition is autosomal dominant Alport syndrome which also causes a mutation in COL4A3 or COL4A4 genes. This affects about 5% of the cases of Alport syndrome. Patients with this type can develop kidney failure later, after the age of 40. Their children have 50% chance of inheriting the mutation [16].

CASE REPORT

A 37-year-old male patient admitted on General medicine department with complaints of short febrile illness on 3 days and with hyponatremia and he had past history on Alport syndrome. This is one of the rare condition that mostly affects in both kidneys and symptoms usually seen as vision problems and hearing defects and also this patient underwent a renal transplantation around 13yrs ago. Now the patient admitted with complaints of hyponatremia with past history of diabetes and hypertension for 13yrs on treatment includes Tab. Glipizide 5mg P/O 1-0-1, Tab. Everolimus 0.75mg P/O 1-0-1, Tab. Cilnidipine 10mg P/O 1-0-1, Tab. Febuxostat 40mg P/O 1-0-0, Tab. Sodium bicarbonate 500mg P/O 1-1-1, his family history- father got this condition around 20-25yrs back on treatment he had the complaints of jaundice and liver problems. In this patient, during the time of admission period his vitals was checked according to follows as: Body temperature: 98.4°F (98.4°F), pulse: 78bpm (72 beats/min), respiratory rate: 20/min (22 breath/min), blood pressure: 130/80mmHg (120/80mmHg), spo2: 98% (95-100%) (Table 1).

Table 1: Laboratory Investigations

SL. No.	Parameters	Test values with dates				
		11/10	12/10	13/10	14/10	15/10
1.	Hemoglobin	13.1				
2.	Total count	4400				
3.	Polymorph	91.1				
4.	Lymphocytes	18				
5.	Monocytes	0.9				
6.	Eosinophils	0.0				
7.	Basophils	0.0				
8.	Platelet count	1.30		1.0		
9.	RBC	4.54				
10.	PCV	38.3				
11.	MCV	84.4				
12.	MCH	28.9				
13.	MCHC	34.2				
14.	RDW	11.8				
15.	ESR	60		58		40
16.	ANC	4010				
17.	AEC	0				
18.	ALC	350				
19.	MPV	10.1				
20.	Amylase	111				
21.	RBS	489				
22.	CRP	53.2				
23.	Lipase	263				
24.	Sodium	128	130	131	133	136
25.	Potassium	4.5				
26.	Total bilirubin	1.88		1.2		
27.	Direct bilirubin	0.49				
28.	Indirect bilirubin	1.39				
29.	AST	60				
30	ALT	46				
31.	ALP	82				
32.	T.P	6.8				
33.	Albumin	3.6				
34.	Globulin	3.2				
35.	A/G ratio	1.12				
36.	Urea	101		120	98	

37.	Creatinine	3.2		3.3	2.1	
38	Uric acid	3.4				

According to urine routine examination report, urine albumin and sugar was elevated during initial period. The patient underwent supportive care and treatment with IV antibiotics. The levels of urea, total bilirubin, ESR, CRP, albumin and creatinine was found to be normal during the hospital stay. The patient made an uneventful recovery. He was discharged on the sixth day.

DISCUSSION

According to the recent studies from kidney foundation we have compared with genetics, Alport syndrome is caused by a genetic defect of type IV collagen which is usually inherited in an X-linked dominant pattern. The most common earliest sign of Alport syndrome is hearing loss and vision problems.The goal of therapy is still in progress that is to be safely lengthen the intervals. The data from experimental and human research indicate this goal can be accomplished effectively with ACE inhibitor treatment achieving optimal results when initiated before GFR begins to decline [17, 18]. Here is a case report of 37-year-old male patient admitted on general medicine department with complaints of fever for three days and with hyponatremia during the hospital stay he got ear infection and watery eyes therefore further managed with ear drops (otorex 2° BD) and eye drops (Tobramycin 2° BD).

CONCLUSION

Alport syndrome is an inherited disease, which means it is passed down through families. It is caused by changes in genes (mutations) to a protein called collagen. In autosomal recessive Alport syndrome men and women are both affected in similar ways. They will have symptoms such as renal failure, eye issues and hearing defects. Autosomal dominant Alport syndrome which also causes a mutation in the COL4A3 or COL4A4 genes. This affects about 5% of the cases of Alport syndrome. Patients with this type can develop kidney failure later, after the age of 40. Their children have 50% chance of inheriting the mutation. However, due to this genetic condition he had underwent a renal transplantation. There is specific therapy according to this condition likeACE inhibitor therapy or ARB therapy is recommended in individuals with Alport syndrome who shows proteinuria and prescribed medicines can be controlled for further management in disease progression [19, 20]. Here the patient was admitted with complaints of fever illness for three days and hyponatremia. Patient was managed with immuno-suppressive agent, calcium channel blockers, anti-hyperglycemic agents, anti-gout medications according to standard treatment guidelines.

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