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A Single-Center Experience in Alport Syndrome

Saritaş Hazen

Aksaray University Medical Faculty, Nephrology Department, Turkey

*Corresponding Author: Saritaş Hazen, Aksaray University Medical Faculty, Nephrology Department, Turkey, Tel.: +905336095661, E-mail: hazensaritas@hotmail.com

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Abstract

Introduction: Alport Syndrome is a hereditary condition that affects the collagen in the basement membrane and is characterized by microscopic hematuria, sensorineural hearing loss, increasing renal dysfunction, and ocular abnormalities. It is more common between the ages of 20 and 30. Men and women are equally affected. However, the prognosis of men is worse than women due to renal failure. The purpose of this study is to evaluate the demographic and clinical findings of patients with Alport Syndrome in our center.

Material and Method: Among 6230 patients admitted to Nephrology outpatient clinic between January 2018 and January 2020, 15 patients previously diagnosed with Alport Syndrome based on clinical and laboratory findings and renal biopsy were retrospectively included in the study.

Results: 15 patients were included in the present study; eight were male and seven were female. The average age of patients was 30.4±8.8 years. The average age of diagnosis was 24.6±7 years. Two patients were diagnosed with ocular findings, one with hearing loss and renal dysfunction, and 12 with renal dysfunction and microscopic hematuria by renal biopsy. Four patients, two women, and two men, had received kidney transplantation from living donors. Six patients were receiving hemodialysis treatment for end-stage renal failure. Three (20%) patients were followed up for stage four, and two (13.3%) patients for stage three chronic kidney disease. Seven (46.7%) patients had ocular findings, nine (60%) had hearing loss, and 12 (80%) had microscopic hematuria. The mean follow-up period of kidney transplant patients after transplantation was five years. Three renal transplant patients maintained normal renal function, and one had stage three CKD.

Discussion: Patients who have microscopic hematuria with ocular and auditory signs should be evaluated for Alport Syndrome. Starting treatment before a decrease in glomerular filtration rate (GFR) can significantly delay progression to renal failure. For this reason, early diagnosis is important.

Keywords: Alport Syndrom, Chronic Kidney Disease, Kidney Transplantation

Introduction

Alport syndrome (AS) is a hereditary condition that presents with microscopic hematuria, sensorineural hearing loss, increasing renal dysfunction, and ocular abnormalities [1-4]. Mutations in the genes COL4A3, COL4A4, and COL4A5, which produce α3, α4, and α5 chains of collagen type IV, a component of the kidney's glomerular basement membrane (GBM), are responsible for AS [5-6]. Depending on the type of mutation they possess, affected patients may exhibit a wide variety of characteristics [7]. GBM division, extracellular matrix deposition and glomerulosclerosis, loss of podocyte, renal fibrosis, and finally end-stage renal disease (ESRD) are all caused by the mutant collagen type IV expression[8]. The incidence is estimated to be 80%-85% in X-linked AS (XLAS), 15% in the autosomal recessive form (ARAS), and 1-5% in autosomal dominant AS (ADAS) [9]. A kidney transplant or dialysis are required in about 50% of affected males before the age of 30, and ESRD affects 90% of them before they are 40 in the X-linked form of Alport syndrome, which is the most prevalent type. The prognosis is better for females diagnosed with X-linked form of AS; ESRD develops in approximately 12% of them until the age of 40 years. In the autosomal recessive type of AS, ESRD may develop prior to the age of 20, whereas in the autosomal dominant type of the disease, ESRD may not typically develop until middle age [10]. Diagnostic criteria include abnormal distributions of α(IV) collagen chains by immunohistochemical staining of the glomerular basement membrane, ultra-structural changes and genetic mutations of COL4A3, COL4A4, or COL4A5, family history, sensorineural hearing loss, characteristic eye findings, and diffuse esophageal leiomyomatosis [11].

Today, unfortunately, there is no treatment option that completely cures AS. Some treatment modalities that have been shown to slow the progression to end-stage chronic kidney disease are on the agenda. These treatment modalities are renin angiotensin aldosterone blockers, mineralocorticoid receptor blockers and sodium-glucose cotransporter 2 inhibitors Drug development studies for the treatment of AS continue [12-15].

The purpose of this study is to evaluate the demographic and clinical findings of patients with Alport Syndrome in our center.

Material and Method

Between January 2018 and January 2020, 15 patients who had previously been diagnosed with Alport Syndrome by renal biopsy among 6230 patients admitted to Siirt State Hospital Nephrology outpatient clinic were retrospectively included in the study. Patients under 18 years of age and over 65 years of age, those with malignancy in any organ system, those with systemic connective tissue disease and those with diabetes mellitus were not included in this study. Age, gender, family history (potential consanguinity), hematuria, proteinuria, hypertension, ocular problems, loss of hearing, or chronic kidney disease, were among the clinical and demographic factors examined. Information about the patients was retrospectively reviewed from the files. Non-Interventional Clinical Research Ethics Committee of Siirt University Rectorate granted ethical approval for this investigation. (Decision number 31.12.2020, 2020/13). The study was conducted following the Declaration of Helsinki.

Data Analysis

The data was analyzed by using SPSS 15.0 software. Frequency and percentage of distribution were used to analyze some demographic characteristics of the patients.

Results

15 patients were included in the present study; eight were male and seven were female. The average age of patients was 30.4±8.8 years. The average age of diagnosis was 24.6±7 years. Patients were diagnosed by renal biopsy. Four (26.7%) female and two male patients received kidney transplantation from living donors. Six (40%) patients received hemodialysis treatment for end-stage renal disease. Four (40%) of the 10 ESRD patients were female, and six (60%) were male. Three (20%) patients were followed up for

stage four, and two (13.3%) patients for stage three chronic kidney disease. The mean follow-up period of kidney transplant patients after transplantation was five years. Three kidney transplant patients maintained normal renal function, while one had stage three CKD.

At the time of diagnosis, 7 (46.7%) patients had ocular findings, 9 (60%) had hearing loss, 12 (80%) had microscopic hematuria, 4 (26.7%) had hypertension, and 7 (46.7%) had proteinuria. Renal biopsy revealed focal segmental glomerulosclerosis in 11 patients and membranoproliferative glomerulonephritis in four patients. Clinical and demographic information about patients included in the present study are summarized in Table 1.

Variables	%
Gender	Female/Male:7/8
Average age	30.4±8.8
Average Age at Diagnosis	24.6±7
Hearing Loss	9 (%60)
Vision Loss	7 (%46.7)
Hematuria	12 (%80)
Proteinuria	7 (%46.7)
Hypertension	12(%80)
Family Story	13 (%85.7)
Parental Kin Marriage	9 (%60)
Hemodialysis	6 (%40)
Kidney Transplant	4 (%26.7)

Table 1: Demographic and clinical properties of patients with Alport syndrome

Discussion

ESRD and increasing renal fibrosis are consequences of the genetic type IV collagen disorder known as AS [11]. AS is a phenotypically and genetically heterogeneous disease. In autosomal recessive Alport Syndrome (ARAS), the disease has a severe course in both men and women [3-16]. Although male patients with XLAS experience severe symptoms, it usually has a much milder course in female patients, and the severity of the disease varies according to the degree of inactivation of the X chromosome [3]. In this study, we planned to analyze the clinical and demographic parameters of patients with AS, including age, gender, possible consanguinity, hematuria, proteinuria, loss of hearing, hypertension, ocular disorder, or chronic kidney problems.

Male and female patients with ARAS have equal rates of renal involvement, and most of them develop ESRD in the second or third decades [3,17]. In our study, the average age of diagnosis was 24.6 ± 7 years.

The disease usually manifests itself in childhood or young adulthood [18]. Renal failure and sensorineural deafness frequently appear by the age of 30 in people with nonsense or missense mutations, reading frame changes, or substantial deletions [19]. The presenting symptom of Alport syndrome is usually hematuria [20]. The initial finding in 12 patients (80%) in our patient group was microscopic hematuria.

Hypertension is a late-developing finding, and its frequency and severity increase with age (21). Although HT was detected in four (26.7%) of our patients at the time of diagnosis, HT developed in twelve (80%) during follow-up.

Proteinuria in Alport Syndrome, independent of the mode of inheritance, points to a higher risk of chronic kidney disease even among the heterozygous carriers [12]. All of the male patients who has XLAS and patients who has ARAS develop proteinuria. Proteinuria is usually mild (1-2 g/day); however, it may be nephrotic in 30% of patients [2,22,23]. Seven of our patients (46.7%) had proteinuria at diagnosis.

Male patients who has XLAS and patients who has ARAS are more at risk for having end-stage renal failure [24,25]. The disease is mild in heterozygous women with XLAS, but some develop ESRD [25]. Ten of our patients (66.7%) developed ESRD. Four patients underwent renal transplantation, and six were on intermittent hemodialysis. Two patients (25%) were followed up for stage three and one patient for stage four chronic kidney disease.

Although most Alport syndrome is diagnosed in men, X-linked disorders affect women twice as often. Although women are usually not diagnosed, renal failure may develop in 30% of women with X-linked Alport syndrome until age 60 [23,26]. In our patient group, two female patients who were siblings were diagnosed with AS at ages 16 and 18. Both of them underwent kidney transplantation. While one female patient is followed up with conventional HD, the other female patient is followed up with stage 4 CKD. AS, a phenotypically and genetically heterogeneous disease, can lead to a severe clinical picture in female patients. Therefore, close follow-up and detailed examination are required in female patients.

It is critical to recognize ocular abnormalities connected to Alport syndrome because, in about 40% of patients, ocular symptoms acts as a warning sign of the illness and occur before proteinuria [27]. Anterior lenticulus is considered pathognomonic for AS. It indicates a poor prognosis and is always associated with rapidly progressive renal failure and hearing loss [27,28]. Ocular changes were present in seven of our patients (46.7%). Up to 80% of people who have AS suffer from high-tone sensorineural deafness, which is one of the syndrome's key characteristics [28]. Auditory symptoms seem to parallel the severity of renal involvement and may be concurrent with ocular symptoms [11,27]. It is uncertain what causes the deafness in people with Alport syndrome. Deafness, on the other hand, is a significant prognostic factor since patients with loss of hearing have a higher risk of developing ESRD than patients without it [29]. Nine of our patients (60%) had bilateral sensorineural hearing loss. Six (66.7%) of the patients with hearing loss developed ESRD. Four of the nine patients were on hemodialysis. 2 patients had renal transplantation.

Patient and renal allograft survival after renal transplantation is comparable between patients with AS and patients who underwent the procedure for different reasons [30,31]. In our study, the average post-transplant follow-up period for renal transplant patients was five years. Three renal allograft patients maintained normal renal function, while one had stage three KBH.

Today, unfortunately, there is no treatment option that completely cures AS. Some treatment modalities that have been shown to slow the progression to end-stage chronic kidney disease are on the agenda. These treatment modalities are renin angiotensin aldosterone blockers, mineralocorticoid receptor blockers and sodium-glucose cotransporter 2 inhibitors Drug development studies for the treatment of AS continue [12-15]. Among these agents, RAAS blockers were used in all patients included in our study.

Conclusion

The main feature of Alport Syndrome is phenotypic heterogeneity resulting in a wide range of renal and extra-renal manifestations. Therefore, the most important step in diagnosis is to suspect the disease. Questioning the family history in patients presenting with hematuria and performing an ophthalmologic examination and hearing tests in case of suspicion are guiding factors in diagnosing Alport syndrome. Electron microscopy demonstrating typical changes in the basement membrane of the glomerulus confirms the diagnosis. Current treatment modalities for AS are not curative. However, if these treatments are started before the glomerular filtration rate (GFR) decreases, progression to kidney failure can be significantly delayed. Therefore, it is important that patients are diagnosed early.

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