

# Kidney Transplantation in Patients With Alport Syndrome

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**Introduction:** The aim of this study was to evaluate the results of kidney transplantation in patients with Alport syndrome.

**Materials and Methods:** A total of 15 patients with Alport syndrome underwent kidney transplantation and the result of their transplantation was compared with the results in patients without Alport Syndrome. Rejection episodes and the presence of anti-glomerular basement membrane (anti-GBM) nephritis were assessed in these patients.

**Results:** Fifteen patients with Alport syndrome were compared with a control group including 212 kidney allograft recipients. One patient with Alport syndrome (6.7%) and 30 controls (14.2%) experienced delayed graft function. Renal artery thrombosis was reported in 1 patient (6.7%) with Alport syndrome and 10 (4.7%) in the control group, which led to nephrectomy in all cases. Acute rejection was confirmed in 2 patients (13.3%) by kidney biopsy and classic treatment yielded relative response. However, they lost their grafts 35 and 44 months after the transplantation. On pathologic examination, no specific finding of anti-GBM nephritis was found. In the control group, 43 cases of acute rejection (20.3%) were reported and 12 patients (5.7%) returned to dialysis. The 1-, 3-, and 5-year graft survival rates were 100%, 92%, and 84% in the patients with Alport syndrome, which was not different from those in the control group ( $P = .53$ ).

**Conclusion:** In spite of the risk of anti-GBM nephritis in the patients with Alport Syndrome, it seems that kidney transplantation can yield favorable results and anti-GBM nephritis is not a common etiology of rejection.

*Keywords: hereditary nephritis, kidney transplantation, anti-glomerular basement membrane antibody*

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## INTRODUCTION

Alport syndrome is a hereditary kidney disease that manifests by glomerular damage, loss of hearing, and visual defects.<sup>(1)</sup> Kidney damage results in chronic kidney failure and emerges the need for dialysis or transplantation.<sup>(2)</sup>

Anti-glomerular basement membrane (GBM) antibody is a cause of immunologic complications in this syndrome and forms as a result of mutations that lead to defects in the  $\alpha$  chain of collagen type IV in the GBM.<sup>(3,4)</sup> Less than 10%

of transplant patients with Alport syndrome experience anti-GBM nephritis.<sup>(5,6)</sup> The immune system of the recipient encounters the GBM antigens after transplantation and produces antibodies against them, resulting in anti-GBM nephritis and allograft failure.<sup>(1,4)</sup> Two cases of anti-GBM nephritis were reported by Shah and colleagues in 1988.<sup>(7)</sup> Since then, several researchers have investigated the clinical outcome of transplantation in these patients.<sup>(8)</sup> They have proposed that the incidence of nephritis following transplantation is less than predicted,

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but immunosuppression may have a role in triggering anti-GBM reaction. We decided to perform this study to determine the results of kidney transplantation in patients with Alport syndrome and compare them with kidney allograft recipients without this syndrome.

## MATERIALS AND METHODS

In a prospective study between 1994 and 2003, we evaluated 15 patients with Alport syndrome (case group) undergoing transplantation at our center and compared their outcomes with the results in our kidney recipients without Alport syndrome. Diagnosis of Alport syndrome was made regarding the criteria proposed by Gubler and colleagues<sup>9)</sup> that included hematuria with or without proteinuria, hypertension, and chronic kidney failure with one of the characteristics below: proved impairment of the kidney, progress to kidney failure in at least one of the relatives, sensory-neural hearing loss in the patients or their kinsmen, and visual impairment. Those patients who underwent nephrectomy due to the complications within the first month of transplantation were excluded.

After transplantation, diuresis and the decrease in serum creatinine and blood urea nitrogen was monitored and diagnostic evaluations were performed in case of kidney dysfunction. All patients received cyclosporine with the initial dose of 9

mg/kg on the first day and 6 mg/kg/d, afterwards. Azathioprine was administered with the dose of 3 mg/kg/d in the first month and 1.5 mg/kg/d to 2 mg/kg/d, afterwards. Instead of azathioprine, some patients received mycophenolate mofetil with the dose of 2 g/d. In addition, pulse of methyl prednisolone succinate was started on with the dose of 10 mg/kg to 15 mg/kg for the first 3 days, and then, prednisolone with the dose of 1 mg/kg was administered, which was slowly tapered.

The survival rate of the kidney allografts and the patients were determined using the Kaplan-Meier method and the log-rank test. A *P* value less than .05 was considered significant.

## RESULTS

During the study period, 352 kidney transplantations were done at our center, of which 15 were in patients (4.3%; 14 men and 1 woman) had Alport syndrome (Table). They all received their transplants from living unrelated donors for the first time and all were negative for hepatitis B antigen and hepatitis C antibody. Therefore, in the control group, we included all of the kidney recipients with the same characteristics. The control group included 212 patients, 123 (58%) of whom were men and 89 (42%) were women. The mean age of the patients was  $31.0 \pm 7.4$  years (range, 20 to 42 years) and  $32.5 \pm 7.9$  years (range, 20 to 42 years) in the case and control

Demographic and Clinical Data of Transplanted Patients With Alport Syndrome\*

Patients	Age	Sex	Underlying Disease	Diuresis After Transplant	Creatinine on the 3rd Posttransplant Day	Arterial Thrombosis	Acute Rejection	Graft Loss	Follow-up, mo	Outcome
1	24	M	...	Early	1.7	N	N	N	54	Fair
2	26	M	...	Early	1.5	N	N	N	72	Fair
3	28	M	...	Early	1.4	N	N	N	30	Fair
4	20	M	HTN	Little	6.7	P	N	P	1	Nephrectomy
5	21	F	...	Early	1.7	N	N	N	76	Fair
6	29	M	...	Delayed	4.9	N	N	N	93	Fair
7	39	M	...	Early	1.6	N	P	P	35	Nonfunctional
8	42	M	...	Early	1.3	N	N	N	112	Fair
9	22	M	VUR	Early	1.7	N	P	P	44	Nonfunctional
10	31	M	...	Early	1.6	N	N	N	64	Fair
11	37	M	...	Early	1.5	N	N	N	102	Fair
12	41	M	...	Early	1.4	N	N	N	96	Fair
13	35	M	...	Early	1.5	N	N	N	65	Fair
14	38	M	...	Early	1.6	N	N	N	29	Fair
15	32	M	...	Early	1.4	N	N	N	30	Fair

\*M indicates male; F, female; HTN, hypertension; VUR, vesicoureteral reflux; N, negative; and P, positive. Ellipses indicate no finding.

groups, respectively. In the control group, causes of kidney failure included glomerulonephritis (34.0%), hypertension (30.7%), diabetes mellitus (11.3%), unknown causes (9.9%), vesicoureteral reflux (8.0%), polycystic kidney (4.2%), and obstructive uropathies (1.9%).

Of 15 patients with Alport syndrome, 13 (86.7%) had early diuresis after transplantation and serum creatinine level decreased to 1.7 mg/dL or less within 3 days after the transplantation. One patient (6.7%) experienced delayed graft function (serum creatinine decreased to 1.7 mg/dL or less within 10 days). Early and delayed graft functions were seen in 180 patients (84.9%) and 30 patients (14.2%) of the control group, respectively. Renal artery thrombosis confirmed by angiography or color Doppler ultrasonography was reported in 1 patient (6.7%) with Alport syndrome and 10 (4.7%) in the control group, which led to nephrectomy.

The patients underwent a total evaluation 1 and 6 months after the transplantation and every 6 months, afterwards. They were followed up for a mean period of  $60.2 \pm 32.1$  months and  $64.1 \pm 38.4$  months in the case and control groups, respectively. Two patients in the case group (13.3%) experienced increased levels of urea and creatinine. Both patients were men (22 years and 39 years). Acute rejection was confirmed by kidney biopsy and classic treatment yielded relative response. However, they lost their grafts 35 and 44 months after the transplantation. On pathologic examination, no specific finding of anti-GBM nephritis was found. The rest of the patients with Alport syndrome did not experience any dysfunction in the transplanted kidney during the follow-up period. No mortality was reported in the case group.

In the control group, 43 cases of acute rejection (20.3%) were reported and 12 patients (5.7%) returned to dialysis (4 within the first, 4 within the second, and 4 within the third posttransplant year), 5 of whom died during the follow-up period. Also, 14 deaths happened in the patients with functioning allografts which were due to car accident and myocardial infarction. The 1-, 3-, and 5-year graft survival rates were 100%, 92%, and 84% in the case group and 98%, 94%, and 90% in the control group ( $P = .53$ ). Patient survival rates at 1, 3, and 5 years were 100% in the case group and 96%, 91%, and 90% in the control group, respectively ( $P = .22$ ).

## DISCUSSION

Genetic mutations in the  $\alpha$  chain of collagen type IV in the GBM results in the X-linked or autosomal recessive Alport syndrome.<sup>(10)</sup> Lack of one or more normal antigens in the  $\alpha$  chain results in an increased possibility of anti-GBM nephritis. Until 1983, more than 100 cases of kidney transplantation in Alport patients had been reported,<sup>(6)</sup> in less than 10% of whom, anti-GBM nephritis occurred.<sup>(5)</sup> Men with deafness and kidney failure before 30 years of age are more susceptible to anti-GBM nephritis.<sup>(11)</sup>

Anti-GBM nephritis occurs within the first year of transplantation or it may last longer to become evident.<sup>(1)</sup> Those patients with antibodies against the membrane are more susceptible to crescent glomerulonephritis and graft loss. Treatment with plasmapheresis and cyclophosphamide are valuable in these patients.<sup>(1)</sup>

Surprisingly, anti-GBM nephritis occurs in few of the patients who receive a kidney allograft. This can be best described by the effect of immunosuppressive therapy to prevent acute rejection which results in less anti-GBM antibody formation, as well.<sup>(6,12,13)</sup> Also, the *COL4A5* gene plays a very important role and patients with mutation in this gene are at a high risk of developing nephritis.<sup>(14-17)</sup> It was shown that 54% of the patients with Alport syndrome and anti-GBM nephritis had deletions in *COL4A5*, while this mutation exists only in 16% of the Alport syndrome population. Less severe defects do not impair expression of the vital parts in the  $\alpha$ -5 chain in the GBM and the antigens will not induce antibody formation. In a study by Shah and colleagues, 2 cases of anti-GBM nephritis were reported 5 months and 18 months after the transplantation. Byrne and associates reported it in 41 patients with Alport syndrome and believed that the occurrence of anti-GBM nephritis in patients with Alport syndrome was less than the predicted value.<sup>(8)</sup> In our study, no case of nephritis was seen and graft survival was similar in the patients of the case and control groups, which argues the results of other studies.<sup>(8)</sup>

We had limitations in our study including the lost-to-follow-up cases, few numbers of the patients, and lack of genetic evaluations. More studies with genetic considerations before the operation, evaluation of the presence of antibody against GBM in the serum

of the patients, and evaluation of the number of the patients with anti-GBM antibody progressing to anti-GBM nephritis are warranted.

## CONCLUSION

Despite the risk of anti-GBM nephritis, we found that in patients with Alport syndrome, kidney transplantation is the method of choice for the treatment of chronic kidney failure, and the risk of graft loss due to anti-GBM antibodies is not a major concern.

## CONFLICT OF INTEREST

None declared.

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