ELSEVIER

Follow-Up of Patients With Juvenile Nephronophthisis After Renal Transplantation: A Single Center Experience

A.C. Tayfur, N. Besbas, Y. Bilginer, F. Ozaltin, A. Duzova, M. Bakkaloglu, F.T. Aki, S. Ozen, R. Topaloglu, and A. Bakkaloglu

ABSTRACT

Background. Nephronophthisis (NPHP) is the most common genetic cause of end-stage renal disease (ESRD) in the first 3 decades of life. Treatment of patients with NPHP is symptomatic; kidney transplantation is the treatment of choice when ESRD is established. We report herein our center's experience with kidney transplantation for children with juvenile NPHP.

Patients. We retrospectively analyzed medical records of 9 renal transplant recipients with a primary diagnosis of juvenile NPHP confirmed by genetic analysis and/or renal biopsy findings in a single center from 1996 to 2010.

Results. Of the 9 patients, 6 received a living related and 3 a cadaveric donor transplantation. Preemptive renal transplantation was performed in 7 patients. The median age of the patients was 13.38 ± 4.6 years; the median follow-up period was 17 months. Posttransplantation immusuppression comprised corticosteroids, a calcineurin inhibitor, and mycophenolate mofetil or azathioprine. One patient lost his renal graft owing to renal graft thrombosis, and grade II chronic allograft nephropathy was diagnosed by renal biopsy on the 62th day after renal transplantation in another patient. The median glomerular filtration rates after transplantation at 1, 3, and 5 years were 85, 75.2, and 83.2 mL/min/1.73 m^2, respectively.

Conclusion. We observed preserved graft functions for long periods among renal transplant recipients with juvenile NPHP. Chronic allograft nephropathy developed rarely on long follow-up.

Nephronophthisis (NPHP), an autosomal recessive tubulointerstitial nephropathy, accounts for 10%–20% of renal failure cases in childhood. Nephronophthisis is distributed equally among boys and girls with incidences of 0.13 per 10,000 live births in Finland, 1 per 50,000 live births in Canada, and 9 per 8.3 million in the United States.[1–3] The first symptoms of juvenile NPHP generally start at ~6 years of age; end-stage renal disease (ESRD) develops at a mean age of ~13 years.[3–5] Positional cloning has identified mutations in 11 genes (*NPHP1-11*, *NPHP1L*) in NPHP.[4] Treatment of patients with NPHP is symptomatic; kidney transplantation is the treatment of choice for established ESRD. Disease recurrence has never been reported in transplanted kidneys.[3–6] To date, there have been few reports regarding the transplant outcomes of patients with juvenile NPHP. We have reported herein the outcomes of transplant recipients with a primary diagnosis of juvenile NPHP who have been followed at our center.

PATIENTS

From 1996 to 2010, we performed 85 pediatric renal transplantations including the primary diagnosis leading to ESRD of juvenile NPHP in 9 patients (10.5%; 5 boys, 4 girls; Table 1). Five patients were genetically confirmed to have a homozygous *NPHP1* mutation, the remaining 4 patients were diagnosed by clinical observation and renal biopsy findings. The mean age at the initial symptoms of NPHP was 5 ± 3.2 years. The median time between the first symptoms and reaching ESRD was 9 years (range, 1–11.5 years). The mean age of

From the Department of Pediatrics (A.C.T., N.B., Y.B., F.O., A.D., S.O., R.T., A.B.), Pediatric Nephrology Unit, Hacettepe University Faculty of Medicine, Ankara, Turkey; and Department of Urology (M.B., F.T.A.), Hacettepe University Faculty of Medicine, Ankara, Turkey.

Address reprint requests to Nesrin Besbas, MD, Prof. Dr., Hacettepe University Faculty of Medicine, Department of Pediatrics, Pediatric Nephrology Unit, Sihhiye, 06100 Ankara, Turkey. E-mail: nbesbas@hacettepe.edu.tr

0041-1345/–see front matter
doi:10.1016/j.transproceed.2011.01.107

Table 1. Data of the 9 Transplanted Patients with Juvenile Nephronophthisis

Gender (M/F)	5/4
Growth retardation on presentation (%)	88
Renal findings	NB in 1 patient, VUR in 2 patients
Extrarenal findings	RP in 1 patient
Consanguinity (%)	55
Renal disease in relatives (%)	50
Mean age (±SD) at RT (y)	13.38 ± 4.64
Preemptive RT	7
LRD	6
LNRD	0
Cadavers	3
Graft failure	1
Vascular thrombosis	1
Rejection	1
Death	0
Recurrence of original kidney disease	0

NB, neurogenic bladder; VUR, vesicoureteral reflux; RP, retinitis pigmentosa; RT, renal transplantation; LRD, living related donor; LNRD, living nonrelated donor.

the patients at transplantation was 13.38 ± 4.6 years; their median follow-up time after renal transplantation was 17 months (range, 4–82 months). Renal transplantation followed hemodialysis in 2 patients. Six patients recieved a living related parental (LRD) and 3 a cadaveric (CD) donor transplant. Preemptive renal transplantation was performed in 7 patients. Posttransplantation immunosuppression comprised corticosteroids, a calcineurin inhibitor (tacrolimus), and mycophenolate mofetil or azathiopurine (n = 1) with basiliximab induction therapy. One patient with heterozygote factor 5 Leiden mutation and an LRD transplant presented with renal vein thrombosis detected by color Doppler sonography on the first day after transplantation and treated immediately with heparin but required graft nephrectomy on second day owing to the failure of anticoagulation therapy. Grade II chronic allograft nephropathy was diagnosed in 1 patient by renal biopsy, which was performed when the serum creatinine level was 1.65 mg/dL on the 62nd day after transplantation. The patient and graft survival rates were 100% and 88.8% at 1 year, 100% and 88.8% at 3 years, and 100% and 88.8% at 5 years after transplantation, respectively. Eight of 9 patients had functional grafts at the last visit. No primary disease recurrence was observed during follow-up. Median glomerular filtration rates after transplantation at 1, 3, and 5 years were 85, 75.2, and 83.2 mL/min/1.73 m^2, respectively (Figure 1). In 2 patients cytomegalovirus reactivation at 6 months after transplantation was controlled by the use of gancyclovir. The immunosupressant dosages were decreased owing to high BK virus loads in blood and urine in another patient.

DISCUSSION

Juvenile NPHP is one of the most frequent causes of ESRD among children. It invariably leads to ESRD at a median age of 13 years. Treatment of patients with juvenile NPHP is symptomatic; kidney transplantation is the treatment of choice when ESRD is established.[3–6] Reports on renal transplantation outcomes among juvenile NPHP patients suggest excellent outcomes, apart from posttransplantation polyuria, which is a potential risk factor for vascular thrombosis after kidney transplantation; it can persist for months in some patients. Disease recurrence has never been reported among kidneys transplanted for juvenile NPHP. According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), graft survival in patients with NPHP was significantly better than that in patients with other primary diagnoses. Rates of thrombosis and acute and chronic rejection were similar between NPHP and all other patients in the 2006 NAPRTCS database. Polyuria experienced by these patients also did not increase the risk for thrombosis, decrease graft survival, or decrease graft function compared with all patients in the NAPRTCS database.[6]

None of our patients experienced persistent posttransplantation polyuria. One patient with heterozygous factor 5 Leiden mutation and an LRD transplant developed a renal vein thrombosis that was detected with color Doppler sonography on the first day after transplantation. He was treated immediately with heparin but graft nephrectomy was required on the second day. According to the NAPRTCS, vascular thrombosis has become the most common cause (11.6%) of graft loss among index transplants performed from 1996 to 2001.[7] Inherited or acquired thrombophilic risk factors have been associated with an increased incidence of early graft loss, acute rejection (AR) episodes, and impaired renal graft function. Authors recommend to evaluate all risk factors for thrombosis in patients who are candidates for transplantation and to treat those with thrombophilic risk factors with intensified anticoagulation regimens.[7–9]

Grade II chronic allograft nephropathy was diagnosed by renal biopsy on the 62nd day after renal transplanta-

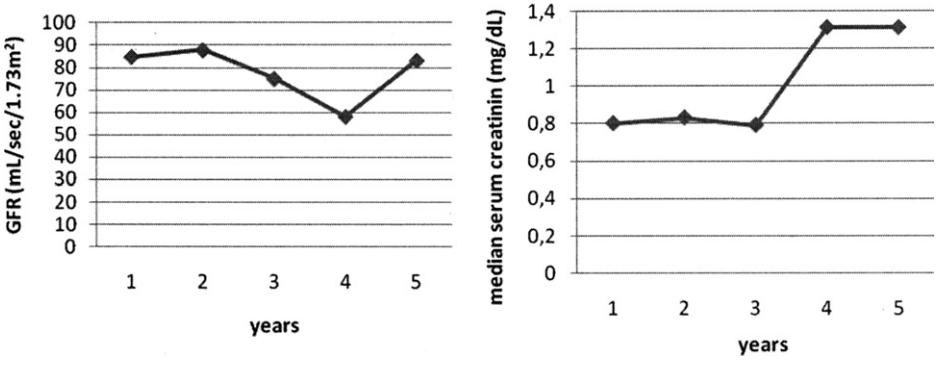

Fig 1. Median glomerular filtration rates (GFR) and median serum creatinine levels of patients according to years after transplantation.

tion in 1 patient. Unsatisfactory compliance and multiple AR episodes have been found to be independent predictors of chronic rejection.[10] The query for compliance to the treatment was satisfactory for this patient. We were unable to predict AR episodes, because we did not perform surveillance biopsies, but the patient has been followed with impaired graft function without further deterioration since 2002.

LRD kidney transplantations are associated with better outcomes and graft survivals than CD transplantations, especially when performed preemptively.[11,12] In our database, 6 patients received a parental LRD transplant and preemptive renal transplantation was performed in 7 patients. The excellent outcome of our transplanted NPHP patients was attributable partly to the use of potent immunosuppressive agents and induction therapy, to better compliance, to regular monitoring of drug levels and cytomegalovirus and polyoma virus replication, to appropriate therapy for infections, to high rates of LRD kidney transplants, and preemptive transplantation among 9 patients. Disease recurrence was not observed in renal grafts.

In summary, we observed that the renal graft function was preserved for long periods among renal transplant recipients with juvenile NPHP. Chronic allograft nephropathy may develop rarely upon long follow-up.

REFERENCES

1. Potter DE, Holliday MA, Piel CF, et al: Treatment of end-stage renal disease in children: a 15-year experience. Kidney Int 18:103, 1980

2. Pistor K, Olbing H, Scharer K: Children with chronic renal failure in the Federal Republic of Germany: I. Epidemiology, modes of treatment, survival. Arbeitsgemeinschaft fur Pädiatrische Nephrologie. Clin Nephrol 23:272, 1985

3. Hildebrandt F, Zhou W: Nephronophthisis-associated ciliopathies. J Am Soc Nephrol 18:1855, 2007

4. Wolf MT, Hildebrandt F: Nephronophthisis. Pediatr Nephrol 26:181, 2011

5. Salomon R, Saunier S, Niaudet P: Nephronophthisis. Pediatr Nephrol 24:2333, 2009

6. Hamiwka LA, Midgley JP, Wade AW, et al: Outcomes of kidney transplantation in children with nephronophthisis: an analysis of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry. Pediatr Transplantation 12:878, 2008

7. McDonald RA, Smith JM, Stablein D, et al: Pretransplant peritoneal dialysis and graft thrombosis following pediatric kidney transplantation: a NAPRTCS report. Pediatr Transplant 7:204, 2003

8. Kranz B, Vester U, Nadalin S, et al: Outcome after kidney transplantation in children with thrombotic risk factors. Pediatr Transplant 10:788, 2006

9. Bilginer Y, Topaloglu R, Aki FT, et al: Outcome of primary glomerular disease in pediatric renal transplantation: a single-center experience. Transplant Proc 40:129, 2008

10. Tejani A, Ho PL, Emmett L, et al, North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Reduction in acute rejections decreases chronic rejection graft failure in children: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Am J Transplant 2:142, 2002

11. Liem YS, Weimar W: Early living-donor kidney transplantation: a review of the associated survival benefit. Transplantation 87:317, 2009

12. Shapiro R, Sarwal MM: Pediatric kidney transplantation. Pediatr Clin North Am 57:393, 2010