The Turkish Journal of Pediatrics 1996; 38: 345-348

ADVANCES IN THE CLINICAL MANAGEMENT OF PEDIATRIC KIDNEY TRANSPLANTATION*

Ümit Saatçi MD**

SUMMARY: Saatçi Ü. (Nephrology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Advances in the clinical management of pediatric kidney transplantation. Turk J Pediatr 1996; 38: 345-348.

Renal transplantation is the best form of renal replacement therapy for children reaching end-stage renal failure. The first human transplantation was performed by Dr. Voronoy from a cadaver donor in 1933; however, because of the lack of immunological laboratory assessments, this transplantation resulted in rejection. Progress in immunological evaluation and new immunosuppressive drugs have improved survival in renal transplantation.

The first renal transplantation in Turkey was performed by Dr. Haberal et al. on November 3, 1975. This child was one of five siblings with juvenile nephronophytisis, and the mother was the donor. Dr. Haberal has thus pioneered renal transplantation in Turkey. In the following years Dr. Haberal initiated cadavral transplantation in our country in collaboration with Eurotransplant. He has also contributed to the law concerning transplantation in Turkey. Subsequently many transplantation centers have been developed in the country. In spite of marked progress in transplantation technology, pediatric transplantation has not improved as fast as adult transplantation. This is due to several factors, such as the difference in the etiological factors leading to chronic renal failure, technical factors, growth and sexual development, factors relevant to infections and vaccinations, and psychological problems. *Key words: renal transplantation, children.*

Renal transplantation is the best mode of renal replacement therapy. The first renal transplant in humans was performed in 1933 by Dr. Voronoy from a cadaver donor[1]. However, because of the lack of immunological laboratory assessments, this graft resulted in rejection. Improvement in histocompatibility matching, immunosuppressive therapy, improved peri- and post-operative care as well as the diagnosis and treatment of rejection have all contributed to better patient survival and graft outcome in renal transplantation. The first transplantation in Turkey was performed in 1975 by Dr. Haberal at Hacettepe University Faculty of Medicine. The first cadavral transplantation was done in collaboration with Eurotransplant, again by Dr. Haberal[2,3]. There are now more than 25 years of accumulated experience with renal transplantation in children, but the survival rates have not reached those of adults. According to the registry of United Network

* From the Nephrology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Professor of Pediatrics and Pediatric Nephrologist, Hacettepe University Faculty of Medicine.

for Organ Sharing Scientific Renal Transplantation, the one-year graft survival rate is poorer in recipients under the age of 16[4]. Recipient age less than two, donor age less than six, prior transplantation, lack of anti-thymocyte globulin (ATG)/anti-lymphocyte globulin (ALG)/OKT3 therapy, a history of greater than five transfusions, HLA-DR mismatches, and low cyclosporine-A (cys) levels are the reported factors for graft failure in children[5].

However, the survival rate of transplanted children is greater than for those on dialysis programs. Psychological and physiological rehabilitation in particular is better in transplanted patients.

Congenital urinary system defects constitute one of the major causes of renal failure in children, whereas in adults diabetic nephropathy and glomerulopathies are the leading causes. Congenital urinary tract malformations were the cause in 42 percent of end-stage renal disease (ESRD) patients in one study[6]. Vesico-ureteral reflux (VUR) and posterior urethral valves are the most frequent abnormalities. In our department these were found to be the etiology in 47 percent of the population with end-stage renal disease. In the past, children with abnormal lower urinary tracts were not considered suitable candidates for a renal transplant. However, bladder reconstructions are now being performed in preparation for subsequent renal transplantation[7,8].

Growth failure is prominent in children due to multisystem dysfunctions introduced by the uremic state. Although quality of life has been much improved in these children, growth retardation remains a problem. Growth is indirectly correlated with the age of transplantation, whereas it is directly correlated with glomerular filtration rate (GFR). Rejection episodes delay the growth process. Growth is affected by corticosteroids alone, despite normal renal function. Lower doses and alternate day schedules lessen the effect. However, supra-physiological doses of growth hormone (GH) serum to be effective in promoting growth. A marked increase in growth velocity has been established by the use of this hormone in transplanted children[9]. However, there are controversies regarding the deleterious effect of growth hormone on renal function. It has been suggested that it causes glomerulosclerosis by hyperfiltration. GH also affects the immunological system and interferes with other immunosuppressive treatments, enhancing allograft rejection[9].

Infections remain a major cause of morbidity and mortality in transplant patients; however, many infections can be successfully prevented by immunization. The Committee on Infectious Diseases recommends that live attenuated vaccines not be given until three months after immunosuppressive therapy has been terminated[10]. Cytomegalovirus (CMV) is a herpes virus, and OKT3 and ALG have increased the risk of CMV disease. Vaccination provides only poor seroconversion

and incomplete protection. Live attenuated CMV vaccine is given about eight weeks prior to transplantation[11]. Although CMV infection is not prevented by vaccination, the infections that occur in a CMV-seropositive donor are modified. While this vaccine has been successful in adults, studies in children are lacking[10]. Other medical measures in dealing with CMV infection include acyclovir, interferon, ganciclovir and CMV hyperimmunoglobulin.

Varicella is a well-recognised problem for children who are immunocompromised[12]. Seronegative children who are to be transplanted must be vaccinated by attenuated varicella vaccine[13].

Hepatitis C in renal transplant patients is an increasing problem in the pediatric population. To prevent hepatitis C virus (HCV) infection, several measures can be useful, such as avoiding blood transfusions, isolation of anti-HCV (+) patients and performing liver biopsies in patients who are (+) for HCV RNA. Transplantation from HCV-positive donors to negative recipients should be avoided. Patients with evidence of chronic liver disease and detectable HCV RNA can be treated with ribavirin or interferon[14].

Renal transplantation of patients with hepatitis B infection has been tempered by a concern that immunosuppression may lead to viral replication and progressive liver damage. HBsAg positive patients treated with Cys have a better outcome than those treated with azathiopyrine. Post Cys-era HBsAg positivity is not a contra-indication to renal transplantation[15]. Children who do not have HBsAg and antibodies should be immunized prior to transplantation.

Malignancies are increased in transplanted patients due to immunosuppressives. Non-Hodgkin's lymphoma, Kaposi sarcoma and skin cancers are associated with this therapy[16].

Conditions known to be associated with recurrence of disease in transplanted kidneys can be responsible for graft failure[17]. FK506 and cyclosporine regimens are equally effective in maintaining excellent graft function in pediatric renal transplant recipients. Advantages of the FK506 regimen include less hirsutism and gingival hypertrophy. It also reduces the risk of hypertension more than steroids do. FK506 monotherapy may alleviate the persistent growth failure by the avoidance of steroids; its steroid-sparing effects may be of particular importance in the pediatric population[18]. Recently Cys G (OG 37-324) has been reported to be an efficacious immunosuppressant with less nephrotoxicity than Cys A. Cys A and G appear to have similar efficacy; however, objective parameters of renal function demonstrated less nephrotoxicity with the use of Cys G[19]. The available data show that it is possible to use Cys A as monotherapy for maintenance immunosuppression of renal transplantation patients. However, the data also indicate that caution must be exercised and that doubts remain

which must be clarified. Further controlled and randomized trials must be done to answer the questions about this therapy[20].

REFERENCES

1. Hamilton DN, Reid WA. Yu Yu Voronoy and the first human kidney allograft. Surg Gynecol Obstet 1984; 159: 289-294.
2. Haberal M. Transplantation in Turkey. Transplant Proc 1993; 25: 2352-2353.
3. Haberal M. Historical evolution of kidney and liver transplantation in Turkey. Transplant Proc 1995; 27: 2771-2774.
4. Ettenger RB. Children are different: the challenges of pediatric renal transplantation. Am J Kidney Dis 1992; 20: 668-672.
5. Tejani A, Sullivan EK, Fine RN, Harmon W, Alexander S. Steady improvement in renal allograft survival among North American children. Kidney Int 1995; 48: 551-553.
6. Gradus D, Ettenger RB. Renal transplantation in children. Pediatr Clin North Am 1982; 29: 1013-1038.
7. Dykes EH, Ransley PG. Gastrocystoplasty in children. Br J Urol 1992; 69: 91-95.
8. Koyle MA, Pfister RR, Kam I, et al. Bladder reconstruction with the dilated ureter for renal transplantation. Transplant Proc 1994; 26: 35-36.
9. Inguilli E, Tejani A. An analytical uvieux of growth hormone studies in children after renal transplantation. Pediatr Nephrol 1995; 9: 61-65.
10. Gershon AA. Immunizations for pediatric transplant patients. Kidney Int Suppl 1993; 43: 587-590.
11. Newstead CG. Cytomegalovirus disease in renal transplantation. Nephrol Dial Transplant 1995; 10 (Suppl 1): 68-73.
12. Feldman S, Hughes W, Daniel C. Varicella in children with cancer: 77 cases. Pediatrics 1975; 80: 388-397.
13. Zamora I, Simoń JM, Da Silva ME, Piqueras AI. Attenuated varicella virus vaccine in children with renal transplants. Pediatr Nephrol 1994; 8: 190-192.
14. Maroles JM. Hepatitis C and renal transplantation: outcome of patients. Nephrol Dial Transplant 1995; 10 (Suppl 6): 125-128.
15. Nelson SR, Snowden SA, Sutherland S, Smith HM, Parsons V, Bewick M. Outcome of renal transplantation in hepatitis BsAg positive patients. Nephrol Dial Transplant 1994; 9: 1320-1323.
16. Brunner FP, Landais P, Selwood NH. Malignancies after transplantation. The EDTA-ERA registry experience. Nephrol Dial Transplant 1995; 10 (Suppl 1): 74-80.
17. Davisom AM. Renal transplantation: recurrence of original disease with particular reference to primary glomerulonephritis. Nephrol Dial Transplant 1995; 10 (Suppl 1): 81-84.
18. Ellis D, Shapiro R, Jordan ML, et al. Comparison of FK-506 and cyclosporine regimens in pediatric renal transplantation. Pediatr Nephrol 1994; 8: 193-200.
19. Henry ML, Elkhammos EA, Davies EA, Ferguson RM. A clinical trial of cyclosporine G in cadaveric renal transplantation. Pediatr Nephrol 1995; 9: S49-S51.
20. Ponticelli C, Opelz G. Are corticosteroids really necessary in renal transplantation? Nephrol Dial Transplant 1995; 10: 1587-1592.