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Long-term follow up of renal function and histology after renal allograft transplantation in early childhood

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Abstract Survival rates, renal function, and histopathology were evaluated in 49 prospectively followed patients transplanted under 5 years of age at our center. Most patients (84%) suffered from congenital nephrosis of the Finnish type. Triple immunosuppression with cyclosporine administered in three daily doses to pre-school children was used. Patient survival 7 years after transplantation was 98% and graft survival 88%. All graft losses were due to post-transplantation nephrosis. The proportion of pathological findings in the follow-up biopsies did not change substantially with time. Five years after transplantation, 47% showed a normal histology and after 7 years this rose to 67%. Mean glomerular filtration rate (GFR) was 68 and 55 ml min per 1.73 m^2 5 years and 7 years, respectively, after transplantation. The decline in GFR with time was significant. We conclude that good long-term results can be achieved with individually tailored triple immunosuppression in the youngest age group, even with cadaveric donors.

Key words Kidney transplantation · Small children · Graft survival · Function · Histopathology

Introduction

Kidney transplantation (Tx) has become the treatment of choice for children with end-stage renal disease. The outcome of kidney Tx in children has improved, but low recipient age is a well known risk factor [11]. Living, related donor (LRD) survival rates equal to those in older children have been reported [7], but the outcome of cadaveric (CAD) Tx in small children is usually less favorable [1].

We report survival rates, renal function, and histopathology in 49 prospectively followed patients transplanted at < 5 years of age, between 1987 and 1997.

Patients and methods

All kidney allograft recipients under 5 years of age receiving their first graft at our center were included in the study. Triple immunosuppression (cyclosporine, azathioprine and methylprednisolone) with cyclosporine administered in three daily doses to pre-school children was used [6]. The patients were followed prospectively and studied for renal function and histopathology 1.5, 3 ,5, and 7 years after Tx.

Percutaneous renal core needle biopsies were performed under ultrasound guidance using an automated punch device (Bioptycut).The biopsies were analyzed according to the Banff classification of kidney transplant pathology [9] and examined independently by two investigators (E. Q. and L. K.), without knowledge of kidney function. Glomerular filtration rate (GFR) was measured by ^{51}Cr-EDTA clearance.

Actuarial survival analysis, log-rank test, paired and unpaired *t*-tests were used for statistical analysis. A P value < 0.05 was considered significant.

The study design was approved by the Ethical Committee of the Children's Hospital at the University of Helsinki and informed consent was obtained from parents or patients prior to their inclusion in the study.

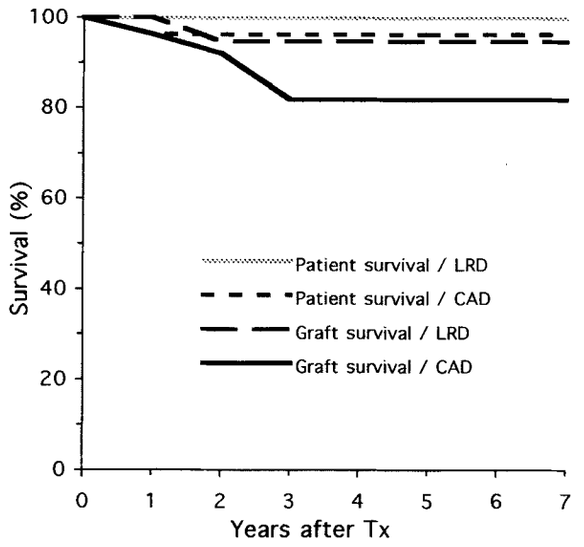

Fig. 1 Primary patient and graft survival in children < 5 years of age at the time of renal transplantation (*LRD* living, related donor, *CAD* cadaveric donor, *Tx* transplantation)

Table 1 Patient and donor characteristics (*CNF* congenital nephrosis of the Finnish type, *obstr. urop.* obstructive uropathies, *LRD* living, related donor, *CAD* cadaveric donor)

Diagnosis	*n*	Gender	*n*	Donor	*n*
CNF	41	Female	18	LRD	20
Obstr. urop.	4	Male	31	CAD	29
Other	4				
Total	49		49		49

Table 2 Distribution of chronic allograft nephropathy in recipients according to the Banff classification [9] (*grade I* mild, *grade II* moderate, *grade III* severe chronic transplant nephropathy)

Years after transplantation	Normal	Grade I	Grade II	Grade III	Total
1.5	17	6	2	1	26
3	15	6	5	–	26
5	9	7	3	–	19
7	6	1	2	–	9

Results

Patient and donor characteristics are summarized in Table 1. Mean time on dialysis was 1.0 year (SD 0.7), mean age at Tx was 2.3 years (SD 1.1), and 53% of the patients were grafted before the age of 2 years. Mean donor age was 29.4 years (SD 12.9) and mean cold ischemia time for CAD recipients, 23.7 h (SD 6.6). The mean number of mismatches were 1.4 (SD 0.7) for AB and 0.7 (SD 0.5) for DR.

Patient survival 7 years after Tx was 100% for LRD recipients and 96.3% for CAD recipients. Graft survival was 94.7% for LRD recipients and 81.8% for CAD recipients (*P* not significant; Fig. 1). Five grafts were lost (four CAD, one LRD) in the congenital nephrosis of the Finnish type (CNF) group due to post-transplantation nephrosis [5].

The proportion of pathological findings in the biopsies did not change substantially with time; 65% showed a normal histology at 1.5 years, 58% at 3 years, 47% at 5 years, and 67% at 7 years after Tx. Thus, the overall histopathology remained quite stable (Table 2). Signs of severe cyclosporine toxicity were rarely seen.

Mean GFR (and SD) 1.5, 3, 5, and 7 years after Tx was 76.3 (23.0), 72.5 (23.1), 67.7 (19.8), and 55.2 (20.6) ml/min per 1.73 m^2, respectively. The decline in GFR with time was significant after 3 years of follow up. GFR was significantly higher in the LRD group than in the CAD group 1.5 years after Tx (85.5 and 67.2 ml/min per 1.73 m^2, respectively, $P < 0.05$), but the difference between the groups diminished with time.

Discussion

Young age is considered to be a risk factor for renal transplantation [11]. However, excellent survival rates have been reported in small children with sequential therapy [2]. Five years after transplantation, 77–86% of children transplanted under 5 years of age have a functioning graft, which is similar to results obtained in older children. Reports from centers using tacrolimus [8] have also been encouraging, but detailed long-term results in small children are still missing. However, with few exceptions [3], 5-year graft survival is less favorable if CAD donors are used in small children and survival varies between 38 and 44% [1, 10]. Our experience with individually tailored triple immunosuppression shows that excellent long-term results can be achieved in children receiving a CAD kidney in early life. Graft survival was 82% 7 years after Tx. In addition, all graft losses were due to a rapidly progressing chronic rejection after a post-transplant nephrosis in CNF patients [5]. The pathophysiology of this complication is still unknown, but no child lost its graft due to an acute or a classic chronic rejection.

The follow-up biopsy findings were also surprisingly mild and stable with time. Between 47% and 67% of our patients had a normal histology and the pathological findings were mostly mild. No trend for increasing pathology with time could be documented. Signs of severe cyclosporine toxicity were also absent.

However , when performing a renal transplantation to a small child, one must aim at sufficient renal function for decades to guarantee normal life and development. Although the GFRs in our patients 5–7 years after

transplantation were comparable to those previously reported after 1–2 years [4], there was a decline in renal function with time. Whether this was due to slowly developing chronic rejection, to a too high cyclosporine dose after the first years, or to other factors, is unknown. There is today general agreement that sufficient immunosuppression at the time of, and shortly after, Tx reduces the number of severe acute rejections, which has a positive impact on later graft function. However, it is not clear what is the optimal dose of cyclosporine or tacrolimus in the long term, as both drugs also influence renal function. In addition, it is possible that an adult graft does not have the same capacity to increase in function with time as would the child's own healthy kidneys.

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