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End-stage renal failure in children younger than 6 years: renal transplantation is the therapy of choice

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Abstract Between 1975 and 1994, 46 children under 6 years of age received a total of 52 renal transplants. Obstructive uropathy and dysplasia accounted for most causes of terminal renal failure (17 and 12 cases respectively). Four patients required a second, 1 patient a third transplantation. Cadaveric organs were used on 33 occasions; 19 patients received a living-related donor kidney. Immunosuppression was performed with azathioprine in 5, with cyclosporine A in 21 and combined azathioprine/cyclosporine therapy in 20 cases. After 1 year, graft survival was 81%, and after 5 years 78%. Creatinine clearance declined slightly between 1 and 5 years from 69 to 56 ml/min per 1.73 m^2. Main causes of graft failure were thrombotic complications in 6 cases and death with functioning graft in 5 cases. Graft thrombosis occurred only in grafts from young donors under the age of 7 years and after vascular anastomosis to the iliac vessels. Only two transplants were lost in rejection episodes. Patient survival was 94% after 1 and 90% after 5 years. Two patients died due to septiacemia, 1 died of a ruptured aortic aneurysm, 1 of cerebral ischaemia and 1 suddenly of unknown cause. Patient and graft survival was not different compared with 204 patients aged 6–16 years who received a renal transplantation during the same time period at our institution. After transplantation the patients receiving cyclosporine A showed a marked catch-up growth in the 1st year. The median standard deviation score (SDS) of body length improved from −2.63 to −1.39 standard deviations.

Conclusion Renal transplantation is the treatment of choice in end-stage renal failure in children under 6 years.

Key words Kidney transplantation · Graft survival · Infant · Children preschool

Abbreviations *CAD* cadaveric donor · *LRD* living related donor

Introduction

Renal transplantation is regarded the therapy of choice in end-stage renal failure in adults and older children. In contrast, the treatment of infants and young children remains controversial. Some authors reported excellent results with renal transplantation [12, 16] whereas others discussed poor outcome after cadaveric donor (CAD) transplantation and increased incidence of graft vessel thrombosis [9].

We analysed the data of 46 children who underwent a first renal transplantation at an age under 6 years in our centre. The results were compared with those from 204 children aged 6–16 years who received a renal transplantation during the same time period.

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Patients and methods

Between 1975 and 1994, a total of 250 children received a renal transplantation at our institution, 46 being younger than 6 years. Young children were treated more frequently in the recent years, in which the proportion of living-related donor (LRD) grafts increased steadily (Fig. 1).

Of the patients, 31 were boys (67.3%). Median age at transplantation was 3.2 years (range 0.8–5.9 years); median weight was 11.7 kg (range 7.5–19.9 kg). Seven patients were transplanted preemptively, i.e. did not receive dialysis treatment prior to transplantation. In the remainder the median dialysis time was 0.8 years (range 0.1–3.8 years). Haemodialysis was performed in 7 patients, peritoneal dialysis in 27 patients and both in 5 cases.

The most common underlying disease was obstructive uropathy. Of these 16 children, 15 were boys reflecting a high incidence of urethral valves. Congenital abnormalities such as hypoplasia/dysplasia and congenital nephrotic syndrome were present in 14 (6 boys) and acquired renal diseases were in 11 patients (mesangial sclerosis 3, focal segmental glomerulosclerosis 5, haemolytic uraemic syndrome 3).

The 46 patients received a total of 52 transplants; 4 patients required a second graft, 1 girl a third one. CAD kidneys were used 33 times; 19 patients received a LRD kidney (11 mothers and 8 fathers).

Grafts were placed intraperitoneally in 15 cases, the others extraperitoneally in the iliac fossa.

Donor age was younger than 5 years in 8 cases. Since 1988, we have hesitated to accept organs from donors younger than 5 years of age since those had a worse outcome compared to older donor ages [10]. In addition, heparin infusion (200 U/kg per day) was introduced in the 2 weeks following transplantation to prevent graft vessel thrombosis.

Until 1981 immunosuppression was routinely performed with azathioprine 2 mg/kg per day and prednisolone 60 mg/m^2 per day, which was tapered to 10 mg/day. Since then we used cyclosporine A (500 mg/m^2/day) orally in two doses together with prednisolone (60 mg/m^2/day), in the initial phase after renal transplantation. In the following weeks cyclosporine was adjusted to blood levels and steroids were tapered to 4 mg/m^2 per day within 7 weeks. Whole blood cyclosporine levels were measured with the EMIT assay (Syva, San José, CA/USA); blood levels of 150–200 ng/ml were considered appropriate in the first 3 months following transplantation and 80–140 ng/ml thereafter. Azathioprine was added if cyclosporine adsorption was unstable or in patients with increased risk of rejection. Out of our 46 patients younger than 6 years, 5 were treated with azathioprine and steroids, 21 received cyclosporine A and steroids, whereas 20 patients were on triple therapy. The immunosuppressive protocol and the proportion of patients treated with triple therapy were comparable in the age group 6–16 years.

Rejection episodes were diagnosed by clinical criteria or proven by biopsy. Treatment of acute rejection consisted of an intravenous high dose prednisolone pulse (10 mg/kg for 6 days). Steroid resistant rejections were treated with OKT 3 monoclonal antibody (0.1 mg/kg for 10 days). The outcome after the first transplantation was retrospectively analysed. Patients below 6 years of age were compared with 204 children 6–16 years old, who underwent a renal transplantation during the same time period and under the same circumstances at our unit.

Mean observation time after renal transplantation was 55 months, ranging from 2 to 235 months.

Neuropsychological status was assessed with the Denver development test in children younger than 5 years; thereafter children were not further tested in case of appropriate school performance.

Patient and graft survival of the first grafts were calculated using the Kaplan-Meier analysis. Growth values were converted to standard deviation scores according to German reference values [2] and compared using the student-t-test.

Results

The survival rate of transplanted children below 6 years is shown in Fig. 2. Actuarial survival rate was 94% after the 1st year and 90% after 5 years. These results did not differ from older children. Actuarial graft survival for the first graft was 81% after 1 and 78% after 5 years (Fig. 3). Again these results were not significantly different from older children.

LRD grafts performed better than CAD grafts without reaching statistical significance (Fig. 4). The difference was mainly due to the fact that early graft losses did not occur with LRD grafts.

Transplant function remained almost stable beyond the 1st year after transplantation (Fig. 5). Glomerular filtration rate calculated from plasma creatinine and body length [21] declined slightly from 69 to 56 ml/min per 1.73 m^2 between 1 and 5 years after the first transplantation.

Rejection episodes occurred in 19 patients (41.5%), of which 5 were steroid resistant and responded to OKT 3 treatment. All in all 0.68 rejection episodes per patient were observed.

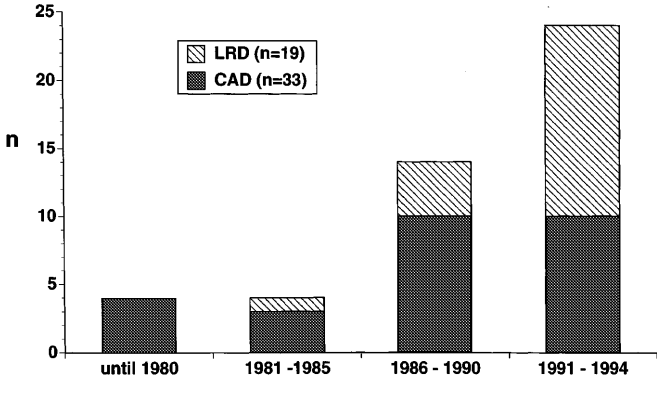

Fig. 1 Renal transplantations in children younger than 6 years from 1975 to 1994 (Medical School Hannover, Germany)

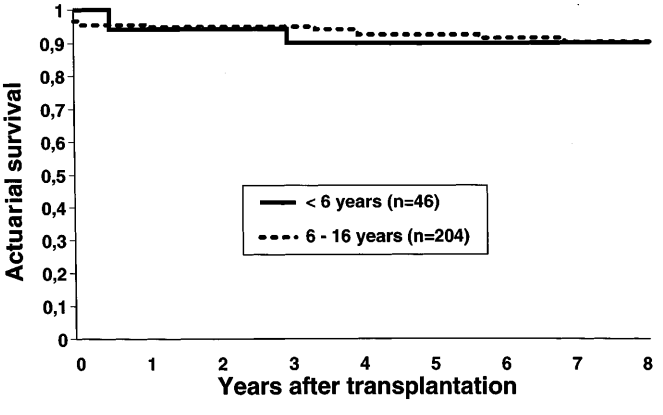

Fig. 2 Patient survival after renal transplantation. Children younger than 6 years versus children 6–16 years old

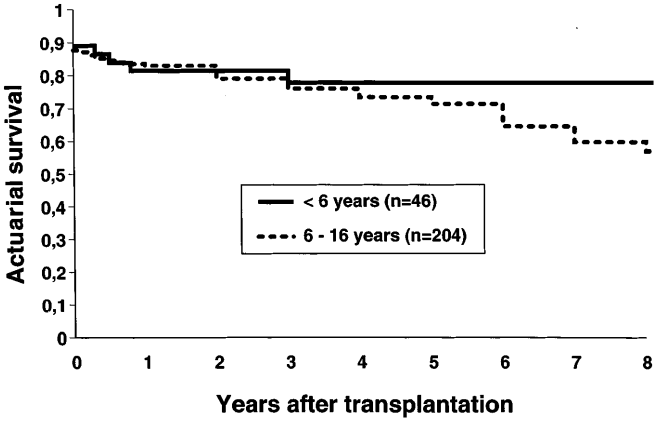

Fig. 3 Actuarial graft survival after first renal transplantation. Children younger than 6 years versus children 6–16 years old

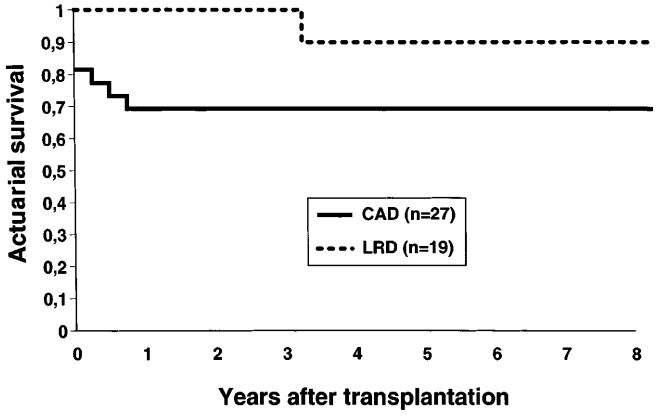

Fig. 4 Actuarial graft survival after first renal transplantation. CAD versus LRD grafts in children below 6 years of age

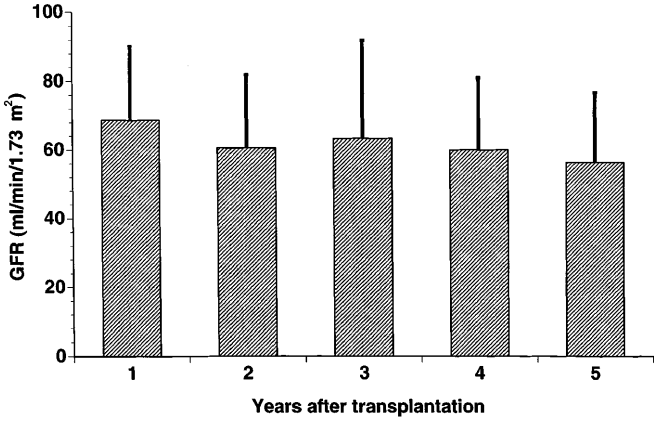

Fig. 5 Glomerular filtration rate 1–5 years after the first renal transplantation (median and SD)

Thirteen grafts were lost including 1 second graft during the whole observation period. The main reasons for graft loss were thrombotic complications in 6 and death of the patient in 5 cases. Death resulted from septicaemia in 2 cases, one each died of a ruptured aortic aneurysm 8 years after transplantation, cerebral ischaemia and sudden unexplained death. Two grafts were lost due to steroid resistant rejection at a time before OKT 3 was available. Recurrent disease was never observed. The grafts lost due to thrombotic events were from very young donors (neonate up to 7 years). Another risk factor for graft thrombosis was the surgical procedure. Grafts with vascular anastomosis to the aorta and vena cava performed better than those using the iliac vessels (actuarial 1 year graft survival 90% vs 63%, $P < 0.05$).

Hypertension was observed in 23% of the patients before and in 56% 1 year and 5 years after transplantation without correlation to cyclosporine usage.

Growth showed significant improvement in the 1st year after transplantation in patients receiving cyclosporine A immunosuppresion (improvement in SDS from −2.63 to −1.39, $P < 0.05$). Thereafter the growth rate remained stable without further catch-up growth. Neuropsychological development in our patients was satisfactory except in two cases who showed severe retardation before transplantation.

Discussion

The negative effects of renal failure during early childhood, especially retarded growth and neurological development, are well documented [17, 19, 20]. Successful renal transplantation improves cognitive and psychomotor function as well as cephalic growth [4]. However, results of renal transplantation have been less encouraging in infants and young children than in older patients. Recently the European registry has reported a 5-year graft survival rate in children under 5 year of 52% [3]. Young age was also identified as risk factor for graft failure in the report of the North American Pediatric Renal Transplant Cooperative Study [22]. CAD transplantation seemed to be especially troublesome in younger children [5]. Increased incidence of graft loss due to vascular thrombosis in younger children has been reported [9]. However, in recent years excellent results of renal transplantation have been reported in children under 5 [12, 13, 16]. In a large series from Minnesota, Najarian and coworkers [15] reported a 5-year graft survival rate using LRD of 73% in 75 infants under 2 years of age.

Our data support the concept of performing renal transplantation in very young children. Results between preschool children and older patients were comparable. This extends also to CAD organs. Several reasons may account for this success: first of all surgical techniques have been adapted to smaller patients. Transplant thrombosis, which was the most prevalent factor leading to graft failure, was exclusively observed with vascular anastomosis to the iliac vessels in our patients. A second factor was donor age. Since we stopped accepting donors younger than 5 years we have not seen a single graft thrombosis emphasizing the use of adult or older

paediatric organ donors. In addition, low dose heparin therapy (200 U/kg/day) is given to every patient for 14 days. Peri-operative problems could be minimized using the retroperitoneal approach even in small children (less than 10 kg) with adult donor kidneys. Graft biopsy is facilitated in this way, bleeding or urine leakage will be restricted to the extraperitoneal space. Today we perform renal transplantations in smaller children in the iliac fossa with arterial anatomosis to the distal abdominal aorta and venous anastomosis to the distal vena cava [7].

Immunosuppression in infants and toddlers is complicated by the increased metabolism and unstable absorption of cyclosporine in this age group [11]. Increased immunoreactivity in these patients with a higher incidence of rejection has been reported by Ettenger et al. [6]. In contrast our patients did not experience a higher rate of rejection; only 0.68 episodes per patients were observed, and only two grafts were lost due to steroid resistant rejection. Only in 41.5% of our patients was a rejection episode observed, this is less than the reported incidence in 1550 children from North America [14]. Since the introduction of OKT 3 into the therapeutic battery we did not lose a single graft in young children due to acute, irreversible rejection. Close monitoring of blood cyclosporine levels and the use of additional immunosuppression may have contributed to this positive result.

Development in our transplanted children was encouraging. Catch-up growth was observed in the 1st year after transplantation in the cyclosporine group. Thereafter and in patients with conventional immunosuppression, growth rate was parallel to the standard curve, while growth retardation remained unchanged. Similar findings were seen during treatment of growth hormone deficiency [18]. Neuropsychological development was satisfying in most cases, two severely retarded patients did not exhibit improvement after successful renal transplantation.

After transplantation, hypertension was observed in 56% of the patients. Compared with older children this prevalence is low [1, 8]. This could be explained with the low incidence of acquired renal disease and a low percentage of hypertension before transplantation.

We conclude that renal transplantation in children under the age of 6 years can be performed with similar results as in older age groups. Graft thrombosis which is a major threat could be avoided using donors older than 5 years and a surgical approach with vascular anastomosis to the distal aorta and vena cava instead of the iliac vessels. Severe rejection episodes were no more frequent than in older age groups when immunosuppression is closely monitored and extended if indicated. We strongly recommend renal transplantation in all infants and pre-school children with chronic renal failure as early as possible. Since the surgical approach and medical therapy in these age group requires special skills, specialized centres should be identified where these patients are treated.

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