Pediatr Nephrol (1999) 13:730–736

ORIGINAL ARTICLE

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Renal transplantation in children under 5 years of age

Received: 19 August 1998 / Revised: 18 November 1998 / Accepted: 18 November 1998

Abstract Between March 1987 and December 1997, 59 renal transplants [49 cadaveric, 10 live related (LRD)], were performed in 54 children aged 5 years and younger. Six children required a second transplant. The median (range) age of the recipients was 2.9 (1.4–5.0) years; mean weight was 12.6 kg (7.4–23) and donor age 11 (2–50) years. Immunosuppression was cyclosporin or FK506, prednisolone, and azathioprine. Antithymocyte globulin was given as induction therapy for second transplants. Patient survival was 98.3%; 1 patient died from upper gastrointestinal haemorrhage. Graft survival was 67.7% at 1 year, 57.4% at 5 years, and 45.2% at 10 years. No LRD graft was lost during 7 years of follow-up. Thrombosis was the main cause of graft loss (10 cases) followed by vascular rejection (2 cases). There was no significant difference in graft survival between recipients aged less than 2, 2–3, and 3–5 years. The height standard deviation score (±SD) improved from –2.1±1.3 at transplantation to –1.0±1.3 at 1 year, –1.1±1.5 at 5 years, and to –0.14±1.1 at 10 years.

Key words Transplantation · Donor age · Recipient age · Thrombosis · Growth

Introduction

Renal transplantation presents a number of challenges, especially in the younger age group [1]. Technical difficulties that predispose to an increased risk of graft vessel thrombosis, particularly in those receiving kidneys from young donors [1, 2], and metabolic and immunological [3, 4] factors contribute to decreased graft survival in very young children. Immunosuppression in infants and toddlers is complicated by the increased metabolism and variable absorption of cyclosporin [5], in addition to hyperimmune reactivity [3. 4]. Nevertheless, there are recent reports of excellent results using both live-related donors (LRD) and cadaveric (CAD) grafts [6–8] and transplantation remains the preferred treatment for end-stage renal failure (ESRF) in young children [7], offering the best potential for good quality of life [9], growth [10] and development [11]. We have reported previously our experience with CAD renal transplantation and medium-term graft survival [12]. In this study we report 10 years of experience in children transplanted before the age of 5 years.

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Patients and methods

Between March 1987 and December 1997, 59 renal transplants were performed in 54 children (44 males). Six patients lost their first grafts and required a second transplant (1 patient had his first transplant at another centre). The median (range) age of the recipients was 2.9 (1.4–5.0) years (mean 3.0 years) and 33 were 3 years or under. Their median (range) weight was 12.6 kg (7.4–23.0). CAD donors were used in 49 children, and 10 were LRD. LRD grafts were donated by a parent (6 from mothers). The median (range) age of all donors was 11 (2–50) years, LRD 31 (31–43) years and CAD 10 (2–50) years.

Seven patients underwent bilateral and 4 unilateral native nephrectomies before transplantation. Five had an unilateral right nephrectomy at the time of transplantation. Forty-five patients (76%) had received dialysis (37 peritoneal dialysis, 8 haemodialysis) for a mean (range) duration of 13.5 (1–31) months before transplantation. Fourteen (24%) were transplanted pre-emptively. Thirteen patients had preformed HLA antibodies pre transplant [median panel reactivity (range) 4.0 (2–64)%]. Major histocompatibility complex mismatches (mean ± SD) were 1.0±0.64 for A antigens, 1.7±0.59 for B antigens and 0.85±0.66 for DR antigens.

Primary renal diseases were: renal dysplasia (RD) (17), posterior urethral valve (PUV) (13), vesico-ureteric reflux and RD (9), congenital nephrotic syndrome (7), tubulo-interstitial disease (1), haemolytic uraemic syndrome (1), Drash syndrome (1), autosomal recessive polycystic kidney disease (1), Wilms tumour (1), cortical necrosis (1), focal segmental glomerular sclerosis (1) and idiopathic crescentic nephritis (1).

CAD donor age was less than 5 years in 10 transplants (22.4%), 5–10 years in 14 transplants (28.6%), 10–30 years in 20 transplants (40.8%), 32 and 50 years in 2 further transplants and unknown in 3 transplants. After 1994, kidneys from donors aged less than 3 years were not used.

Grafts were placed intraperitoneally in 19 cases, or extraperitoneally in the iliac fossa. The venous anastomosis was between the donor renal vein and distal vena cava (n=54) or right common iliac vein (n=5). An end-to-side arterial anastomosis was fashioned between the donor renal artery and aortic patch and the recipient's distal aorta (n=55) or common iliac artery (n=4).

Cold ischaemia time (mean ± SD) was 15.5 (±7.3) h, warm ischaemia time 14.9 (±13.2) min, and anastomosis time 54.3 (±16.3) min. Peri-operative antibiotics (ciprofloxacin) were given with the pre-medication and continued until a negative culture was obtained from the transplant transport medium.

Triple immunosuppression was used in all children, as follows: cyclosporin A intravenously (i.v.), 50 mg/m^2 pre-operatively, then i.v. then orally (p.o.) when tolerated to maintain blood levels within the therapeutic range (150–250 µmol/l); methylprednisolone 600 mg/m^2 (i.v.) pre-operatively, then p.o. prednisolone (or equivalent i.v.) 60 mg/m^2 per day, tapering to 10 mg/m^2 per day by 4 weeks, 5 mg/m^2 per day by 8 weeks, and 10 mg/m^2 on alternate days by 12 weeks; and azathioprine (i.v. then p.o.) 45 mg/m^2 per day. Two patients received FK506 instead of cyclosporin A, initially i.v. 0.06 mg/kg per 24 h, then p.o. 0.2 mg/kg twice a day, adjusted to achieve a therapeutic range of 10–20 ng/ml during the 1st month post transplant, and 5–10 ng/ml following that. The 6 patients who had a second transplant received prophylactic i.v. Merieux antithymocyte globulin (ATG) at a dose of 2 mg/kg i.v. pre-operatively and daily for 9 days post-operatively.

The diagnosis of rejection was based on a rise in plasma creatinine of 10% above the patient's established baseline, with or without oliguria, fever, graft swelling and tenderness, after other causes of renal dysfunction, such as infection, surgical problems or cyclosporin A toxicity, had been excluded. In uncertain cases, needle biopsy was performed. Rejection episodes were treated with prednisolone 3 mg/kg per day for 3 days. Steroid-resistant rejection was treated with ATG.

After 1994 post-operative subcutaneous low-dose heparin (dose given three times daily: children with weight <15 kg 1,000 units, <20 kg 1,500 units, 20–40 kg 2,500 units) was used. Prophylactic ranitidine (an H_2 receptor antagonist) was used in patients transplanted after 1995 for approximately the 1st month. From 1996, co-trimoxazole was used for the first 6 months post transplant as prophylaxis against pneumocystis and urinary tract infection (UTI).

Actuarial graft survival rates were obtained by Kaplan-Meier analysis for all CAD transplants. Life-table analysis was used for LRD transplants because of the small numbers. Log-rank test was used to evaluate the difference between age groups. Height standard deviation score (Ht SDS) was calculated at the time of transplant and at yearly intervals thereafter for children with at least 1 year of transplant function. Student's t-test and chi-squared test were used for statistical analysis. Analysis of variance was used to compare glomerular filtration rate (GFR) data from the same children at different time points. Logistic regression analysis was used to investigate the effect of HLA mismatching on graft loss and early rejection episodes.

Results

Patient survival

Patient survival was 98.3% at 1 year; 1 patient, aged 3.0 years, died with a functioning graft on day 48 post transplant from severe upper gastro-intestinal haemorrhage. She had a haematemesis and melaena on day 33 post transplant. Endoscopy showed a large chronic duodenal ulcer in the first part of the duodenum, just distal to the pylorus. She underwent pyloroplasty and vagotomy, and was well for 10 days post-operatively on total parental nutrition, until she had a further fatal haematemesis. There were no further later fatalities.

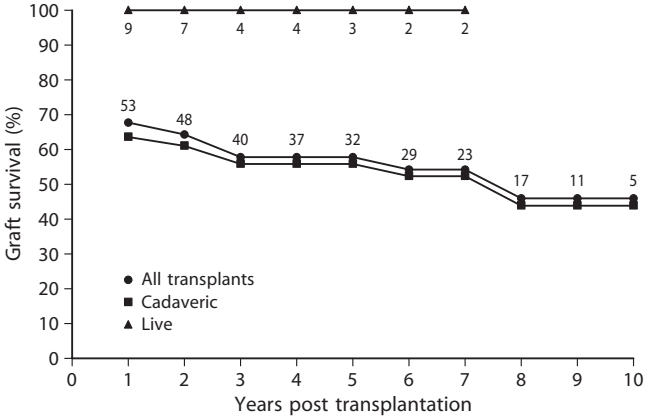

Fig. 1 Actuarial graft survival of all transplants for children engrafted at or under 5 years of age. Number of patients at each time point is shown

Actuarial graft survival (Fig. 1)

CAD graft survival was 63.2% at 1 year (n=44), 55.7% at 5 years (n=29) and 43.5% at 10 years (n=5). After April 1991, 10 children received LRD transplants. Graft survival was 100% at 7 years (n=2). Thirteen CAD grafts were lost during the first 3 months post transplant: 10 from thrombosis without rejection (7 venous and 3 arterial), 2 from acute vascular rejection with associated thrombosis and 1 from chronic vascular rejection. One child had a successful venous embolectomy on the 2nd day post transplant. His graft is functioning to date (5 years post transplant). Five grafts were lost from chronic rejection, 1 each at 2, 3 and 5 years, and 2 at 8 years.

Donor age (Fig. 2)

The mean CAD donor age for recipients who lost their grafts within 3 months was 6.6 (range 2–11) years, which was significantly lower than those with functioning grafts over the same time period [donor age 13.1 (range 3–50) years, P=0.03]. When CAD donor age was divided into under 5 years, 5–10 years, and over 10 years, graft survival from donors over 10 years was significantly better by 3 months [90.5% (95% confidence interval (CI) 77.9–100%), chi-squared=4.7, P<0.05]. At 1 year, the graft survival for donors over 10 years was 79.8% (95% CI 62.1–97.6%) and was 58.3% (95% CI 40.2–76.4%) in those under 10 years of age, but this difference did not reach significance (P=0.09). The lack of significance could be explained by the small number of cases (hence large CI). There was no difference in graft survival at 3 months (chi-squared=0.004, P>0.05), 1 year (P=0.91) or thereafter between CAD donors younger than 5 years and those of 5–10 years.

Recipient age and weight (Fig. 3)

There was no significant difference in graft survival between CAD recipients aged less than 2 years (n=11), 2–3

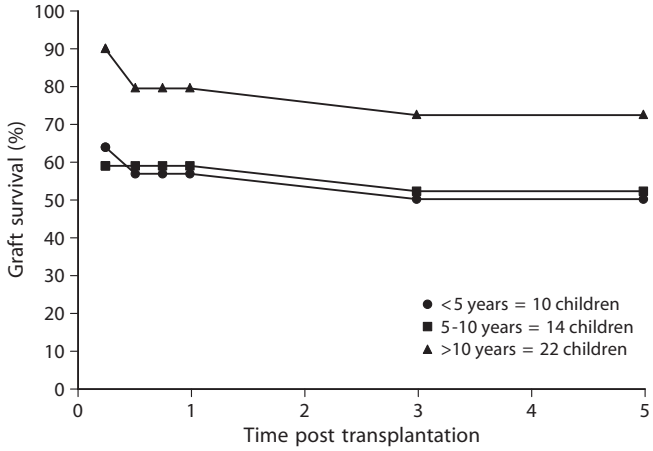

Fig. 2 Cadaveric donor actuarial graft survival subdivided by donor age

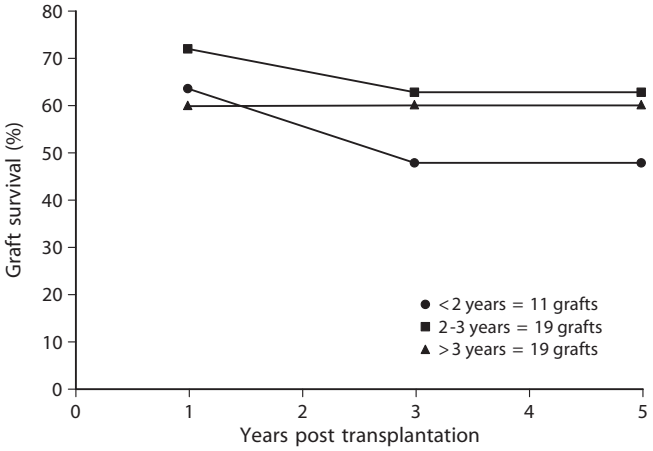

Fig. 3 Cadaveric donor actuarial graft survival subdivided by recipient age

years (*n*=19) and 3–5 years (*n*=19). CAD graft survival in recipients younger than 2 years was 63.6% (95% CI 35.2–92.1%) at 1 year and 47.7% (95% CI 13.3–82.1%) at 5 years. Patient survival in this younger group was 100% at 1 and 5 years. Six patients were transplanted with a weight less than 10 kg, mean (range) 8.9 (7.4–9.8) kg. All but 1 were CAD grafts; 1 lost his graft from venous thrombosis on day 2 post transplant; all the other grafts are still functioning after a mean (range) of 6.8 (3–10) years.

Acute rejection

The peak incidence of acute rejection occurred within the first 3 months post transplant (74%), with an average of 1.0 episode per patient (range 0–4). Median (range) time to first rejection was 8 (2–70) days post transplant. Eight of the rejection episodes were steroid resistant and were treated with a 10-day course of ATG following confirmation of diagnosis by renal biopsy. Eleven patients had 22 late rejection episodes, 9 occurred during the first 12 months and the rest after the 1st year. Twelve patients (20%) were rejection free.

HLA mismatching

There was no significant effect of one or two HLA mismatches of A, B and DR antigens on early graft loss or occurrence of early rejection (within 3 months). However transplant recipients with two or less mismatches (four or more matches) had a significantly better (*P*=0.003) graft survival at 3 months and less early rejection (*P*=0.05). They also had better graft survival at 3 years (*P*=0.02), but at 5 years there was no difference (*P*=0.25).

Growth (Fig. 4)

The mean Ht SDS (±SD) at transplant was –1.84±1.2. Thirty-eight children who had at least 1 year of graft function were evaluated for linear growth. Their Ht SDS at the time of transplant was –1.95±1.2. At 1 year there was a significant improvement (*P*=0.001). Thereafter the improvement was maintained, with an increase at 7 years to –0.39±1.5 (*n*=10) and at 9 years to –0.14±1.1 (*n*=4). One child received 3 years of recombinant human growth hormone, which started 4 years after his second transplant when he was 7 years old. He subsequently required a third transplant at the age of 10.5 years. There was no difference in Ht SDS at the time of transplant between those with short-term follow-up (<4 years) – 1.9±1.3 – or those with longer follow-up (>4 years) – 2.0±1.2, *P*=0.72. Therefore the fall in the number of patients contributing to the height data did not bias the growth data.

Graft function (Fig. 5)

Serum creatinine (mean ± SD) was 71 (44) µmol/l 1 year post transplant, 106 (62) µmol/l at 5 years and 127 (18) µmol/l at 10 years. GFR, calculated from the clearance of ^{51}chromium EDTA [13], was performed annually. Figure 5 shows the mean ± SD values over 8 years post transplant. Graft function declined slowly over the years. The decline in GFR was not significant over the first 4 years (*P*=0.1), but by 5 years (*P*=0.02) and 8 years (*P*=0.0005) it was significant.

Post-operative complications

There was a delay in abdominal closure in 2 children who had their grafts placed intraperitoneally: 1 was closed on the 6th day (recipient weight 10.1 kg, CAD donor aged 16 years); the second after 24 h (recipient weight 11.9 kg, LRD aged 43 years). A third child had abdominal dehiscence that required repair (weight 9.7 kg, CAD donor aged 23 years).

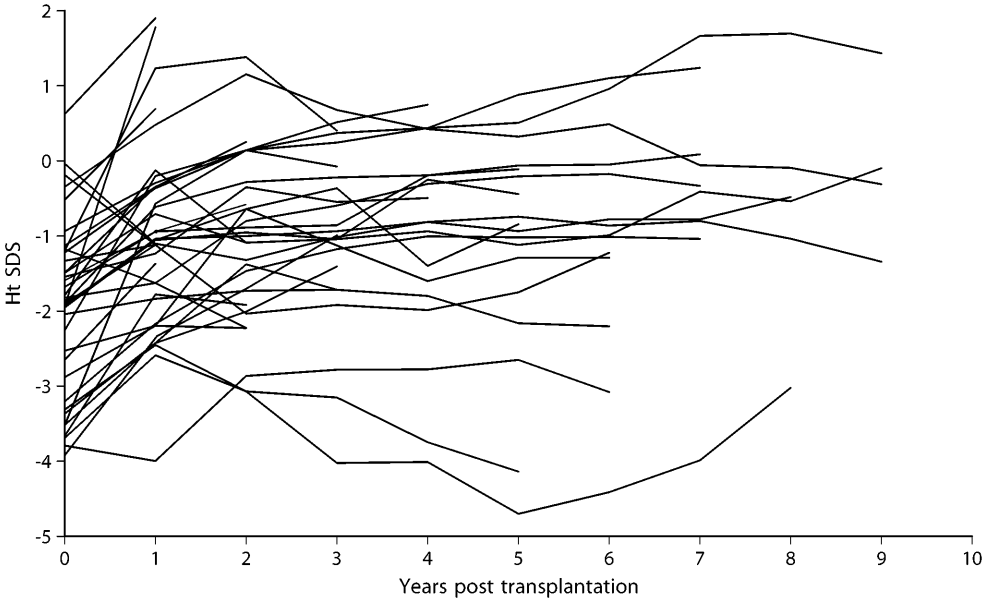

Fig. 4 Individual patients' height standard deviation score (*Ht SDS)* at yearly intervals

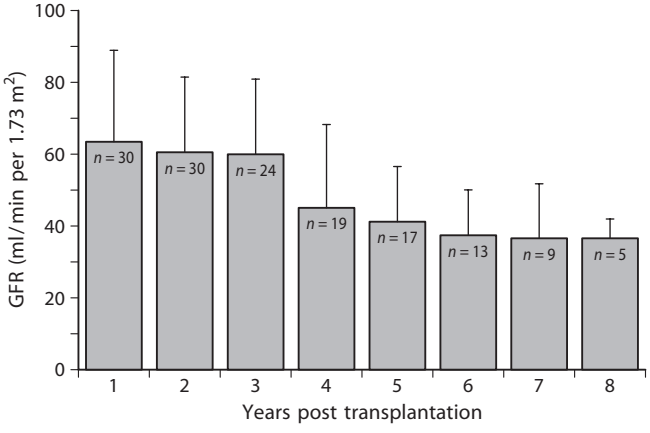

Fig. 5 Glomerular filtration rate (*GFR*) 1–8 years after renal transplantation (mean ± SD)

Ureteric

Three children had ureteric stenoses, and required re-exploration and re-implantation on days 3 and 14 and at 3 months post transplant, respectively. One child required ureteropyelotomy and insertion of a stent on day 23 post transplant for pelvi-ureteric junction obstruction. He lost his graft 2 months later from chronic rejection. An elective ureterocystoplasty was performed 2 years post transplant in 1 child with PUV. Correction of vesico-ureteric reflux in the transplanted kidney by ureteric re-implantation was performed in another child after 2.5 years because of recurrent UTIs and reduced uptake of radiolabelled isotope in the transplant on dimercaptosuccinic acid scan.

Renal artery

One child needed re-exploration and re-anastomosis of a twisted renal artery on the 25th day post transplant. Two children had transplant artery stenoses distal to the origin of the anastomosis, which required balloon angioplasty on day 52 and 4 months, respectively.

Hypertension

Antihypertensive medications were required in 17% of children before transplant, and in 47% in the immediate post-transplant period. One year post transplant, 23% were still on antihypertensive therapy, and 19% at 5 years post transplant.

Infection

Twenty-seven children (6 females) (47%) had a UTI. There was no difference in UTI incidence between females (60%) and males (47.7%), P=0.49. In 11 patients the UTI was within 4 weeks of transplantation. Fifteen children had recurrent UTIs. After the initiation of prophylactic antimicrobial antibiotics in 1996, 3 children had a single UTI and 1 child had two episodes (28.6%), compared with 47.7% before 1996. However this reduction in the incidence of UTI was not statistically significant (P=0.21).

Five children had protracted diarrhoea for more than 2 weeks. Organisms identified were *Cryptosporidium*, adenovirus, astrovirus and enterovirus. Two children had symptomatic cytomegalovirus infection and were treated with gancyclovir 5 mg/kg 12 hourly for 10 days (this dose was reduced to 2.5 mg/kg 12 or 24 hourly with renal impairment). One patient had *Pneumocystis carinii* infection, treated with high-dose co-trimoxazole.

Recurrence of primary disease

One child with congenital nephrotic syndrome (Finnish type) had a recurrence of nephrotic syndrome in his LRD

graft 5 months post transplant. He responded to a course of cyclophosphamide and was in remission for 1.5 years before he had another relapse which responded to prednisolone. Graft function remains good.

Discussion

Successful renal transplantation is the optimal renal replacement therapy for infants and young children with ESRF [14]. It is usually followed by an improvement in growth [10] and psychomotor development [11].

Patient survival in our center is comparable with others [6, 8]. Laine et al. [6] reported 100% patient survival at 3 years and Najarian et al. [8] 97% at 1 and 3 years, and 95% at 5 years. However others have reported less-impressive outcomes [7], particularly in infants [15]. Tejani et al. [15] reported a mortality rate of 17.5% in recipients under 1 year of age, and 8% in 2- to 5-year olds. Englund et al. [16] reported that 17% of those aged less than 7 years had died by 1 year and, in a later paper, that 5 infants of 21 (23.8%) died during the first 6 months post transplant [17]. These results may be affected by the primary renal disease and other associated, co-morbid conditions.

Comparison of graft survival between centres is affected by the proportion of LRDs, which vary from 17% in this centre to 46% in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) [18], 50% in the Finnish study [6], 63% in Germany [7], 71% of the infants reported from Sweden [17], 23% of the European (EDTA-ERA) registry [19] and 74% of those in the study of Najarian et al. [8]. It is clear that LRD graft survival is superior to that of CAD donors [1, 18]. No LRD graft was lost in 10 transplants in this centre over 7 years. LRD graft survival for other studies has been reported as follows: 100% at 1 year and 89% at 3 years [6], 88% for recipients aged less than 7 years at 1 year [1], 75% for recipients aged less than 1 year and 83% for 2- to 5-year-olds at 3 years [18], and 87% in those less than 2 years of age at 5 years [17]. Only two reports have shown no difference between LRD and CAD: Vester et al. [7] reported total graft survival of 81% at 1 year and 78% at 5 years for both LRD and CAD, and Laine et al. [6] reported 100% graft survival at 1 year for both LRD and CAD, although this had fallen to 89% for LRD at 3 years and 73% for CAD.

It might be expected that large donor kidneys (and, therefore, LRDs) would result in surgical complications, such as difficulty in closure of the abdomen after surgery. Although this did occur in 3 children, there were no lasting adverse effects. However, the proportion of LRDs used in this centre is small compared with others.

CAD graft survival rates of 63.2% at 1 year and 55.7% at 5 years are comparable to other studies: 51% at 3 years for children aged less than 1 year and 65% for those aged 2–5 years [18]; 36% at 1 year in recipients less than 7 years [1]; 100% at 1 year and 73% at 3 years for children aged up to 5 years (paediatric CAD donors were only used in 2 transplants in this report) [6]; and 52% at 5 years in children under 5 years of age [19].

The difference in graft survival between LRD and CAD grafts could be explained by the high percentage of early graft loss in CAD grafts secondary to thrombosis. Young donor kidneys transplanted into young recipients are known to be at particular risk of thrombosis [20], and 50% of donors in this report were under 10 years of age. The absence of statistical significance between graft survival from CAD donors over 10 years and 10 years and younger after 3 months despite the presence of a largish difference (79.8% vs. 58.3% at 1 year, 72.6% vs. 51% at 5 and 10 years) could be attributed to the small number of cases. In addition, young children have been demonstrated to have increased immune reactivity compared with adults [3, 4], and therefore can cause irreparable damage to small grafts.

NAPRTCS reported an improvement in patient and allograft survival in young recipients with donors over 6 years of age. The mortality rate for patients less than 2 years of age transplanted in 1992 decreased to 3.6% from a previous average of 15%, and the incidence of thrombosis decreased [18]. Schurman and McEnery [1] reported 1-year CAD graft survival for children less than 7 years of 36%, with the worst outcome of 28% for those transplanted from donors less than 7 years of age. As a consequence of these findings, we restricted the use of CAD donors to those over 3 years of age in 1994. However, although we have observed a decline in the incidence of thrombosis since then, this has not reached statistical significance. It may be possible to use younger donors with heparinisation to decrease the risk of graft thrombosis [21]. In 1994 routine heparinisation of all transplants was initiated for the first 10 days post-operatively, regardless of donor age, but numbers are too small to detect any significant benefit from this.

There was no difference in graft survival when this cohort was subdivided into recipient age less than 2 years, 2–3 years, or 3–5 years. In contrast, NAPRTCS suggests that children less than 2 years of age are at particularly high risk for graft failure [18]. However, Najarian et al. [8] did not find a difference in patient or graft survival between children aged less than 1 year, 1–2 years and 2–5 years. Tyden et al. [17] reported graft survival at 5 years of 44% for CAD and 87% for LRD grafts in infants aged less than 2 years. Patient and graft survival in recipients less than 2 years did not differ from the rest of the group. Although we prefer to transplant children when their weight is 10 kg or above, the outcome of those transplanted at a lower weight was encouraging.

It has been shown that long-term graft survival correlates with the incidence of early rejection [22]. For this reason, many centres use induction therapy with ATG/ALG or OKT3 for all transplants [8, 23]. NAPRTCS reported that 48% of LRD and CAD recipients received induction therapy [18]. In this series ATG pro-

phylaxis was used only in children with pre-formed HLA antibodies. Despite this, the incidence of acute rejection episodes was comparable to other studies [18, 24], although previous reports give variable results [6, 7, 23].

In our previous report we found a correlation between two HLA-DR mismatches and early graft loss [12]. The absence of correlation between two HLA-DR mismatches and early graft loss in this study is similar to a larger study by Mendez et al. [25]. Cicciarelli an Cho [26] reported that two mismatches or less of HLA A, B and DR antigens was associated with a better short- and long-term outcome than the poorer matches.

Catch-up growth was observed in the 1st year post transplantation, following which 50% of children were within the normal range for height; 70% had reached the normal range by the 3rd year post transplantation. These data are in agreement with other published data and suggest that catch-up growth can be achieved following transplantation in young children [7, 17, 27]. Early use of alternate-day steroids may have contributed to the catch-up growth observed. A number of studies suggest that steroid therapy has a deleterious effect on growth [28] and we have shown previously that alternate-day steroid therapy is less growth suppressive when given after renal transplantation in children of pubertal age [29].

Post transplantation the incidence of hypertension (47%) was not as high as that reported in older children [30]. This is likely to be due to the large proportion of children with congenital structural abnormalities of the kidney, which are usually associated with excessive urinary sodium loss from native kidneys. We have previously reported that UTI occurs in 46% of children transplanted in our centre [31]. This incidence, with the highest proportion occurring during the first 4 weeks, and the high recurrence rate is similar in this younger group to the incidence in all children up to the age of 18 years [31]. The risk of other infections and the incidence of post-operative complications is comparable to other reports [32, 33].

As a result of our experience over the years of the study, we have introduced several changes in the management of our patients: we are more positive in our approach to live donation, we have tried to reduce the incidence of CAD graft thrombosis by refusing young donors and by the routine use of post-operative heparinisation, we have introduced prophylactic ranitidine and antimicrobial prophylaxis for *Pneumocystis* and UTI.

We conclude that patient and graft survival in children transplanted before the age of 5 years compares well with results in older children. LRD transplantation has an excellent outcome and should be promoted. Graft thrombosis remains the major cause of graft failure in this young age group, and could be reduced by avoiding young CAD donors.

Acknowledgement We wish to thank the UK Transplant Support Services Authority for their assistance with statistical analysis.

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LITERATURE ABSTRACTS

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Interferon-alpha in chronic hepatitis C infection in dialysis patients

Am J Kidney Dis (1999) 34:55-60

This study assesses the efficacy and adverse effects of interferon-alpha (IFN-alpha) administered at a dosage of 3 million units three times weekly for 1 year in 17 hemodialysis patients with hepatitic C virus (HCV)-associated chronic hepatitis (biopsy proven). The patients were prospectively followed up for a period of 18 months. Liver biopsy was repeated after 6 months of treatment in 13 patients. Patients were classified according to the histological activity index. Biochemical and virological responses were evaluated at the end (end-of-treatment response) and 6 months after completion of therapy (sustained response). HCV RNA became negative in 76% of the patients after 12 weeks of treatment, in 88% after 12 months of treatment, and in 71% of the patients 6 months after completion of therapy. HCV genotype 4 was found in 60% of our population. Alanine aminotransferase (ALT) levels were initially increased in only 6 patients and normalized in 4 of these patients after 12 weeks of therapy, with end-of-treatment and sustained biochemical responses of 83% and 67%, respectively. Of 13 patients who underwent liver biopsies after 6 months of therapy, 11 patients (85%) showed histological improvement. One patient could not tolerate therapy because of marked lethargy and myalgia; the other patients had minor side effects that did not require discontinuation of treatment. Two patients received a cadaveric renal transplant after 1 year of IFN treatment, and they continued to maintain biochemical and virological responses after a follow-up of 17 and 28 months, respectively.

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Deletions in the mitochondrial DNA and decrease in the oxidative phosphorylation activity of children with Fanconi syndrome secondary to antiblastic therapy

Am J Kidney Dis (1999) 34:98-106

The aim of this study is to verify whether there are deletions in mitochondrial DNA (mtDNA) and disorders in oxidative phosphorylation (Ox-phos) complexes in the pathogenesis of secondary Fanconi syndrome (FS). We studied 18 children with tumors who were previously treated with chemotherapy and were off therapy for at least 1 year. All the children had normal renal function at diagnosis. Only 4 children received ifosfamide (IFO) and platinum compounds. We evaluated renal function, Ox-phos activity measured on platelets, and mtDNA extracted from platelets for all patients. Only 2 patients, both treated with IFO and carboplatinum (CARBO) for Wilms tumor and germ-cell tumor, respectively, developed FS 1 and 3 years after termination of therapy. They had decreased activities of Ox-phos that were statistically significant only for nicotinamide adenine dinucleotide (NAD)-reduced cytochrome-c reductase and cytochrome-c oxidase and specific and unidentified deletions in mtDNA that were not maternally inherited. Our data suggest that treatment with IFO and CARBO might be responsible for deletions in mtDNA, decreased activity of Ox-phos, and impaired rates of transport of D-glucose, phosphate, and amino acids.