PART V

TRANSPLANTATION—CLINICAL ASPECTS

Chairman: Professor J H Thaysen
Renal Transplantation in the Very Young Child

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Summary

Thirteen children, aged between one and five years, received transplants and 11, all related-donor recipients, are alive (mean follow-up 2.2 yr). Five had congenital nephrotic syndrome, 5 had hypoplastic-dysplastic kidneys and one each had polycystic kidneys, nephroblastoma and glomerulonephritis. One child died of peritonitis and one died following irrevocable rejection. Two children required retransplantation. The present serum creatinine of the survivors is 0.67 ± 0.23 (x ± SD) mg/100 ml. Eight of the 11 survivors have shown catch-up growth. Thus we conclude that related-donor transplantation is warranted in children having reached the age of one year and six kilograms in body weight.

Introduction

Dialysis and transplantation are now accepted therapies for adults with end-stage renal failure. Older children are offered these therapeutic alternatives in many centres. However, the technical difficulties inherent in the dialysis and transplantation of very young children have discouraged many transplantation teams from accepting these patients. Several authors have reported the successful transplantation of the small child (Najarian et al, 1971; Belzer et al, 1972; Fine et al, 1973; Swenson et al, 1971; McEnery et al, 1973). Herein we review our experience in the renal transplantation of 13 children between the ages of one and five years. Our results upon follow-up of the 11 survivors for from one to four years and five months indicate that these patients should be considered as excellent candidates for transplantation.

METHODS AND RESULTS

The underlying renal disorders in these 13 children were generally different from
those encountered in adults (Table I); five had hypoplastic-dysplastic kidneys (HDK), five had congenital nephrotic syndrome (CNS), and one each had infantile polycystic kidney disease with congenital hepatic fibrosis, bilateral nephroblastoma (Wilm's tumour) and rapidly progressive glomerulonephritis.

The five children with HDK all had advanced renal failure with a mean serum creatinine (Cr) of 6.6 mg/100 ml (range 4.4–8.8 mg/100 ml). Each child fell well below the −2SD curve for both height and weight for their age. Two children in this group (SJ and MD) had advanced renal rickets and one (MD) had bilateral slipped femoral epiphyses. Four patients in this group required dialysis in preparation for transplantation. Four of these patients had a one-stage surgical procedure consisting of bilateral nephrectomy, splenectomy, and transplantation. One patient (KE) had severe hypertension uncontrollable by dialysis and thus underwent emergency bilateral nephrectomy. Her hypertension resolved immediately and transplantation was carried out two weeks later.

Two of the five children with CNS were in advanced stages of uraemia with Cr values of 11 mg/100 ml (TM) and 7.0 mg/100 ml (GJ) respectively. Two had mild renal insufficiency (KG, Cr 1.0 mg/100 ml, Cr clearance 30 ml/min/1.73 m²; MR, Cr 1.4 mg/100 ml, Cr clearance 22 ml/min/1.73 m²) and were transplanted because of complete failure to thrive and serious recurrent infections. One had moderate uraemia (TF, Cr 3.2 mg/100 ml). Two patients (TM and TF) had a marked diminution in proteinuria as their renal insufficiency progressed and thus were no longer nephrotic at the time of transplantation. Both of these patients had one-stage surgical procedures as outlined above. The two patients with overt nephrotic syndrome and minimal renal insufficiency (KG and MR) initially underwent bilateral nephrectomy and splenectomy. Within two to three weeks of bilateral nephrectomy in KG and MR all laboratory manifestations of the nephrotic syndrome disappeared (Figure 1). One patient (GJ) had both advanced renal failure (Cr 7.0 mg/100 ml) and severe nephrotic syndrome (albumin 1.0 g/100 ml). With vigorous ultrafiltration on haemodialysis he became anuric and the laboratory features of nephrosis reversed.

SG, because of uncontrollable hypertension, and RR, because of bilateral Wilm's tumour, underwent bilateral nephrectomy in preparation for transplantation.

The 12 children requiring haemodialysis prior to transplantation had this procedure performed using techniques previously described (Kjellstrand et al., 1971). Special paediatric shunts (Buselmeier et al., 1971), dialysers (Shideman et al., 1972), dialysis lines and weight monitoring procedures (Kjellstrand et al., 1973) were employed. Calculations of dialysis efficiency, mannitol infusions and high glucose baths were used to avoid severe osmotic shifts and disequilibrium on dialysis (Kjellstrand et al., 1971). One severe dialysis complication occurred.

While in the nephrotic state GJ suffered severe ischaemia to his left forearm and hand following an episode of shunt clotting with propagation of the thrombosis above the brachial artery bifurcation. Ischaemia persisted following shunt removal, thrombectomy and fasciotomy. Streptococcal cellulitis ensued and was successfully
Figure 1. Effects of the anephric state on the reversal of the biochemical manifestations of the nephrotic syndrome. KG and MR underwent bilateral nephrectomy at time 0; GJ became anuric with vigorous dialysis at time 0.

treated. The wound finally closed following several weeks of coverage with pig skin xenografts. However, severe ischaemic signs and pain persisted and two months following transplantation amputation was performed.

In all instances transplantation was carried out by a transperitoneal approach and, with one exception, end-to-side anastomoses between the donor renal artery(ies) and vein(s) and the recipient’s aorta and vena cava (Najarian et al, 1971). In one instance (MD) the inferior vena cava was accidentally severed during transplant nephrectomy and retransplantation. The renal vein of the second transplant kidney was then anastomosed end-to-end to the proximal portion of the cava and the distal cava was ligated. These children received approximately 100 ml of blood just prior to release of the aortic and caval clamps during transplant surgery in order to avoid shock from the shift of relatively large volumes of blood into the transplanted kidney. At the same time they received approximately 1mEq/kg of sodium bicarbonate to obviate lactic acidosis consequent to variable periods of total aortic occlusion.

Technical problems developed in three instances. RR had severe persistent hypertension following transplantation, secondary to renal artery stenosis. Following repair of this lesion he developed peritonitis and died. At autopsy he was found to have metastatic Wilm’s tumour in mediastinal structures. MD developed renal insufficiency 7 months following transplantation, due to chronic rejection and mid-ureteral necrosis, fibrosis and obstruction. Function improved following pyeloureterostomy using the patients original ureter but the transplant failed because of chronic rejection and a second transplant was performed 4 months later. KG developed recurrent pyelonephritis following transplantation. This problem abated following removal of the refluxing stump of her own ureter.
Figure 2. Comparison of patient survival following related-donor transplantation in the 1–5 vs. 6–14 year age groups.

Subsequently, however, recurrent infections with reflux into the transplant ureter developed. She has remained well on long-term nitrofurantoin therapy.

Two patients died; RR following complications described above and BA following irreversable graft rejection 10 weeks after transplantation. Survival of the 12 small children receiving related-donor grafts was compared to that of children ages 6–14 years with related grafts (Figure 2). Very good results were obtained in both groups. The present mean Cr of the successfully transplanted small children is 0.67 ± 0.23 mg/100 ml (x ± SD) (Table I). Detail of problems developing following transplantation are presented in Table I. The mean dose of maintenance immunosuppression is azathioprine, 2.1 mg/kg/day, and prednisone, 0.33 mg/kg/day. Only one child (JL) has been placed on alternate-day prednisone. Otherwise prednisone is taken as a single morning dose.

Growth data in these children is presented in Figures 3 and 4. Of the children growth-retarded at the time of transplantation and now having normal renal function only one has failed to demonstrate catch-up growth. The exception (MD) had severe problems with his first transplant (see above). It is too early after his second transplant to judge whether catch-up growth will occur. One child (PW) has mild renal insufficiency and is growing slowly. SG was normal height at the time of transplantation and is growing at a slightly subnormal rate. The 8 children demonstrating catch-up grew at a mean of 1.9 cm/yr faster than expected for their age.
TABLE I. Summary of Basic Data and Outcome of Transplant Operations for the Thirteen Children

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age at Transplant yr mth</th>
<th>Weight at Transplant (kg)</th>
<th>Time Since Transplant yr mth</th>
<th>Present Cr. (mg/100 ml)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PW</td>
<td>HDK</td>
<td>3 2</td>
<td>9.3</td>
<td>3 2</td>
<td>1.6</td>
<td>CID* in early post-transplant period; mild chronic rejection; hypertension; required correction of slipped femoral epiphysis</td>
</tr>
<tr>
<td>SJ</td>
<td>HDK</td>
<td>5</td>
<td>10.1</td>
<td>4 5</td>
<td>0.6</td>
<td>Well. Severe varicella infection 4 years after transplantation</td>
</tr>
<tr>
<td>KE</td>
<td>HDK</td>
<td>4 11</td>
<td>11.6</td>
<td>2 4</td>
<td>0.8</td>
<td>Well, except for severe sensory-neural hearing loss</td>
</tr>
<tr>
<td>MD</td>
<td>HDK</td>
<td>3 9</td>
<td>9.7</td>
<td>1 6</td>
<td>0.1</td>
<td>Well. Required second transplant. Viral encephalitis before CID* after his second transplant (see text). Will require repair of pre-existing slipped femoral epiphyses</td>
</tr>
<tr>
<td>BA</td>
<td>HDK</td>
<td>1 1</td>
<td>6.5</td>
<td>—</td>
<td>—</td>
<td>Died following rejection 10 weeks after transplantation</td>
</tr>
<tr>
<td>GJ</td>
<td>CNS</td>
<td>2 1</td>
<td>8.0</td>
<td>1</td>
<td>0.4</td>
<td>Well. Amputation of left arm due to shunt accident</td>
</tr>
<tr>
<td>KG</td>
<td>CNS</td>
<td>3 2</td>
<td>11.0</td>
<td>1 6</td>
<td>0.4</td>
<td>Well. Urinary tract infections in post-transplant period (see text)</td>
</tr>
<tr>
<td>TF</td>
<td>CNS</td>
<td>2</td>
<td>9.7</td>
<td>2</td>
<td>0.6</td>
<td>Well</td>
</tr>
<tr>
<td>TM</td>
<td>CNS</td>
<td>4 1</td>
<td>13.5</td>
<td>3</td>
<td>0.6</td>
<td>Well. Rejected 1st transplant from grandmother after 6 weeks. Received cadaver transplant 3 years ago. Recent episode of pneumococcal meningitis; recovered CID* in early post-transplant period</td>
</tr>
<tr>
<td>MR</td>
<td>CNS</td>
<td>2 9</td>
<td>7.9</td>
<td>1 8</td>
<td>0.7</td>
<td>Well, except for mild sensory-neural hearing loss</td>
</tr>
<tr>
<td>SG</td>
<td>Glomerulonephritis</td>
<td>5</td>
<td>13.9</td>
<td>2 1</td>
<td>0.9</td>
<td>Well. Required bilateral femoral osteotomies for repair of genu valgum</td>
</tr>
<tr>
<td>JL</td>
<td>Polycystic Kidneys</td>
<td>1 11</td>
<td>6</td>
<td>2</td>
<td>0.7</td>
<td>Died of peritonitis following repair of renal artery stenosis 4 months following transplantation (see text)</td>
</tr>
<tr>
<td>RR</td>
<td>Wilm’s Tumor</td>
<td>5 2</td>
<td>13.3</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

CID* = cytomegalic inclusion disease
Figure 3. Growth following renal transplantation in boys age 1–5 yr. —— mean; —— 2SD below mean.

Figure 4. Growth following renal transplantation in girls age 1–5 yr. —— mean; —— 2SD below mean.
Many of the children, uraemic or nephrotic from birth, showed significant psycho-motor retardation at the time of transplantation. Without exception, these small children demonstrated rapid and, often, remarkable improvement in intellectual and motor function within a few months of successful transplantation.

**DISCUSSION AND CONCLUSIONS**

Renal transplantation is now an important form of therapy in many centres treating patients with end-stage renal failure. However, technical and ethical considerations and the *a priori* assumption that results would be poor have led to a reluctance to carry out this procedure in the very small child.

The primary renal diseases in the young child differ significantly from those of older children and adults. A large proportion have developmental abnormalities or congenital nephrotic syndrome (CNS), disorders which do not reoccur in the transplanted kidney. The main indication for transplantation in our small children was advanced uraemia. However, two children with CNS had adequate renal function but had total failure to grow and serious recurrent infections despite careful medical management in the year preceding transplantation.

The 12 children dialyzed prior to transplantation tolerated this procedure well. The one major complication, loss of a limb, emphasizes the important risk of thrombotic complications in the nephrotic patient. These patients should have shunts placed as distal as possible from critical arterial bifurcations and the shunts should be replaced if recurrent clotting occurs. Early nephrectomy following the institution of dialysis may, by reversal of the hypercoaguable state associated with nephrosis, diminish the risk of vascular shunt accidents in these patients.

A one-stage bilateral nephrectomy-splenectomy-transplantation procedure was carried out wherever possible in order to avoid two major intra-abdominal procedures. Exceptions in our series included two patients with uncontrollable hypertension, one with bilateral Wilm's tumour and two with overt nephrotic syndrome. It is our strong feeling that the risks involved in transplanting the oedematous, malnourished, hypercoaguable, hypogammaglobulinaemic nephrotic patient are unwarranted. A period of several weeks of dialysis and vigorous nutritional repletion following initial bilateral nephrectomy reduces these risks.

Transplantation of an adult kidney into a child weighing less than 10 kg represents a major challenge to the surgeon but has been successfully carried out at several centres (Najarian et al, 1971; Belzer et al, 1972; Fine et al, 1973; Swenson et al, 1971; McEnery et al, 1973). However, care should be taken to avoid hypovolaemia and acidosis upon removing the aortic cross clamp. With these precautions the small child can provide excellent perfusion to the adult kidney and immediate renal function.

We have emphasized related-donor transplantation in our patients and 11 of
12 patients so treated are well and have good renal function one to four and more years later. Belzer et al transplanted 14 children in this age group (Belzer et al, 1972). Four of five children survived a mean of two years following related-donor transplantation while only 3 of 8 cadaver recipients followed 9 or more months after transplantation survived. Several reports of transplantation in the entire paediatric age group (to age 18 years) confirm the major survival advantage provided by related vs. cadaver transplantation (Najarian et al, 1971; Belzer et al, 1972; Fine et al, 1973). Thus we feel that the willing (often enthusiastic) parent or older sibling be used as the donor wherever possible.

In our small children catch-up growth uniformly occurred in growth-retarded children achieving sustained normal renal function following transplantation. This is in marked contrast to results with older children where, despite successful transplantation and low-dose steroid therapy, significant catch-up growth is much less common (Najarian et al, 1971; Grushkin and Fine, 1973). Grushkin and Fine suggested that bone age less than 12 years was a critical determinant of growth potential following transplantation. Recently, it has been shown that, in children with long-standing renal insufficiency, bone age advances faster than height age (Betts, 1974). Thus the potential for catch-up growth diminishes with time. We do not suggest that children should be transplanted earlier in order to preserve growth potential. However, we do wish to point out that, when transplantation is otherwise indicated in the very young child, excellent growth can be expected with daily low-dose prednisone therapy if good renal function is achieved. We have not explored in depth the use of alternate-day prednisone as a means of promoting growth. It is interesting, however, that in the report of McEnery describing alternate-day therapy, all three children eight years of age or younger showed catch-up growth while only one of five children 10 years of age or older demonstrated this phenomenon on this steroid regimen (McEnery et al, 1973). The three younger children in McEnery’s series grew no faster than did our patients on 0.33 mg/kg of prednisone each morning.

Graft survival and patient survival in our small children compare favourably with those obtained in our older children and in our so-called ‘ideal risk patients’, i.e., related-donor recipients aged between 15 and 45 without evidence of systemic disease. The good growth results, excellent psycho-motor progress and psychologic adaptations of these small children strongly favour related-donor transplantation.

References

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Open discussion

MANNIK (USA) Our experience is somewhat different to yours. We have done eight transplants in children between one-and-a-half and five-and-a-half years. Three were related and five cadaver donors. What happens to the IQ in the patient who is uraemic from birth? In two of our patients who were uraemic from birth mental development improved after transplantation for two years, and after this their IQ stayed at about 70%.

MAUER The small child, transplanted within the first two years of life, tends to have been very sick during that period of time when the brain is still undergoing important development. This is particularly true in congenital nephrotic syndrome, where malnutrition may be a very important component of psycho-motor retardation. In general, successful transplantation results in catch-up in intellectual function. A couple of patients did not reach the mean IQ for their age after two years, but they were greatly improved. Where they will be several years from now is difficult to predict. I would emphasise that of our eleven surviving children, only two have measurable retardation.

CHAIRMAN Did you state the dose of immunosuppressive drugs?

MAUER (See text, Ed). With our maintenance treatment, the growth rates are equivalent to those reported for alternate-day prednisone in children.

F P BRUNNER (Switzerland) Am I correct in assuming that children with congenital nephrotic syndrome didn’t develop nephrosis again in the transplant?

MAUER Yes, I think this is a critical question. None of the six children with congenital nephrotic syndrome have redeveloped proteinuria after transplantation. In contrast, in 75% of our patients with steroid-resistant nephrotic syndrome, that syndrome recurred, suggesting that the abnormality in congenital nephrotic syndrome is a primary abnormality of the glomerular filter.