Renal transplantation in the management of bilateral Wilms’ tumour (BWT) and of Denys–Drash syndrome (DDS)

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Abstract

Background. Wilms’ tumour (WT) occurs bilaterally in \(~5–7\)% of affected children. In some patients, complete surgical removal of the malignant tissue cannot be achieved without bilateral total nephrectomy. In Denys–Drash syndrome (DDS), bilateral nephrectomy is indicated both because of the associated nephropathy usually progressing rapidly to end-stage renal failure and because of the high risk of WT development in any residual renal tissue.

Methods. Case records of patients with a diagnosis of either bilateral WT (BWT) or DDS, who underwent bilateral nephrectomy and subsequent renal transplantation between 1980 and 1996 at the Hospital for Sick Children, London, were reviewed.

Results. Allogeneic renal transplantation was performed in two children with BWT and four with DDS, three of whom had developed unilateral WT by the time their kidneys were removed. Renal transplantation was performed 15–49 months after bilateral nephrectomy at a mean age of 45 (26–76) months, with a minimum of 1 year tumour-free survival after completion of chemotherapy in those with WT. One patient died after renal transplantation. Five children had a favourable outcome, with a mean follow-up of 80 (29–121) months post-renal transplantation.

Conclusion. Advances in dialysis and transplantation programmes for young children offer the potential for a marked improvement in the prognosis for patients with BWT and for those with DDS.

Key words: bilateral Wilms’ tumour; Denys–Drash syndrome; renal transplantation

Introduction

Wilms’ tumour (WT) is one of the commonest intra-abdominal malignancies of childhood, affecting \(~1\) in 10,000 children in Western Europe [1]. The current overall cure rate for unilateral WT exceeds 80\%, but 5–7\% of the affected children present with or develop a tumour in the contralateral kidney [2]. Though most of these patients can be treated successfully with chemotherapy and nephron-sparing surgery (e.g. bilateral partial nephrectomy), some do require total bilateral nephrectomy [3].

Children with Denys–Drash syndrome (DDS) account for <1\% of all patients with WT, and a special management strategy is needed for them. A nephropathy, characterized by varying degrees of focal or diffuse mesangial sclerosis, presenting with proteinuria at an early age and progressing rapidly to end-stage renal failure (ESRF), is common to this syndrome, together with either genital anomalies, WT or both. Due to a high risk of WT development in any residual renal tissue in DDS, bilateral nephrectomy is indicated early in the course of the disease. Thus DDS inevitably leads to a complete loss of functioning renal tissue early in life [4,5].

Consequently, in some patients with bilateral Wilms’ tumour (BWT) and in all those with DDS, bilateral total nephrectomy is necessary. Because of recent advances in dialysis and transplantation programmes for young children, renal replacement therapy and subsequent transplantation are now a realistic option for patients with either of these conditions.

Subjects and methods

Case records of patients with a diagnosis of either BWT or DDS, treated at the Hospital for Sick Children, London, between 1980 and 1996, were reviewed. Those with a history of bilateral nephrectomy and subsequent allogeneic renal transplantation were identified and their case histories reviewed retrospectively.

Case reports

Six patients were identified (Table 1). Two patients (one boy and one girl) suffered from BWT (patients A1 and A2, Table 1) and four children, two of whom
Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>DOB</th>
<th>Sex</th>
<th>Age at presentation (months)</th>
<th>Stage/histology</th>
<th>Chemotherapy prior to surgery</th>
<th>Age at nephrectomy (months)</th>
<th>Age (months) at renal transplantation</th>
<th>Last follow-up (date)/graft survival (months)/renal function (plasma creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Bilateral Wilms’ tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>10/89</td>
<td>male</td>
<td>8</td>
<td>BWT; FH</td>
<td>Vcr + Act-D + Doxo VP16 + Ifo Car + Epi + Vcr + RT</td>
<td>LN (17) partial RN (17)</td>
<td>cadaveric (62)</td>
<td>death after 1 month</td>
</tr>
<tr>
<td>A2</td>
<td>8/91</td>
<td>female</td>
<td>11</td>
<td>BWT; FH</td>
<td>Vcr + Act-D AVD</td>
<td>Vcr + Act-D RHN (15)</td>
<td>live-related (38)</td>
<td>(10/97) 36; Cr 40 μmol/l</td>
</tr>
<tr>
<td>B. Denys–Drash syndrome with or without WT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>6/84</td>
<td>male</td>
<td>18</td>
<td>1; FH no</td>
<td>LN (20) (Wilms’ tumour) RN (prophylactic) (31)</td>
<td>CAD (36)</td>
<td>cadaveric (36)</td>
<td>(06/96) 108; chronic rejection and graft failure necessitating haemodialysis</td>
</tr>
<tr>
<td>B2</td>
<td>3/85</td>
<td>female</td>
<td>21</td>
<td>no Wilm’s tumour</td>
<td>BN (27) (prophylactic)</td>
<td></td>
<td></td>
<td>(11/97) 121; Cr 109 μmol/l</td>
</tr>
<tr>
<td>B3</td>
<td>12/86</td>
<td>male</td>
<td>at birth</td>
<td>1; FH no</td>
<td>LN (11) (Wilms’ tumour) RN (12) (prophylactic)</td>
<td></td>
<td></td>
<td>(11/97) 106; Cr 211 μmol/l</td>
</tr>
<tr>
<td>B4</td>
<td>3/89</td>
<td>female</td>
<td>46</td>
<td>111; FH Vcr + Act-D</td>
<td>LN (WT) (51) (prophylactic)</td>
<td>Vcr + Act-D RHN (55)</td>
<td>live-related (76)</td>
<td>(12/97); 29; Cr 55 μmol/l</td>
</tr>
</tbody>
</table>

Act-D = actinomycin D; AVD = Ifo + etoposide + Doxo; BN = bilateral nephrectomy; Car = carboplatin; Doxo = doxorubicin; Epi = epirubicin; FH = favourable histology; Ifo = ifosfamide; LN = left nephrectomy; RHN = right heminephrectomy; RN = right nephrectomy; RT = radiotherapy; sbm = single base mutation; Vcr = vincristine.
had unilateral WT at presentation, were diagnosed as having DDS (patients B1–B4, Table 1). A third infant with DDS with perineal hypospadias and bilateral undescended testes from birth (patient B3) developed unilateral WT at the age of 10 months. Five of the six children presented during the first 2 years of their life with abdominal swelling, haematuria or nephrotic syndrome. Two children also presented with hypertension (patients A1 and B2). WT was diagnosed by renal ultrasound, abdominal computerized tomography (CT) scan and tumour biopsy. Staging investigations were performed and treatment prescribed according to the UKCCSG (United Kingdom Children’s Cancer Study Group) Wilms’ Tumour Study protocols [6] and histopathological classification as defined by the National Wilms’ Tumour Study Group [7]. All WTs were of ‘favourable’ histology. Three children with WT were started on chemotherapy in order to reduce tumour bulk prior to surgical intervention. In patient A1, initial triple chemotherapy with vincristine (Vcr), actinomycin D (Act-D) and doxorubicin (Doxo) failed to reduce the size of the tumour mass, and other regimens [VP16+ifosfamide (Ifo) or carboplatin (Car)+epirubicin (Epi)+Vcr] were used until surgery 8 months from diagnosis. Usually, chemotherapy was continued for a total of 6–12 months.

Following removal of one kidney and partial contralateral nephrectomy, both patients with BWT had had recurrence of the tumour in the remaining renal tissue after intervals of 5 and 3 months. In a further attempt to reduce tumour bulk, individual treatment regimens were designed. They were treated with either radiotherapy (3000 cGy; patient A1) or a triple chemotherapy [AVD regime (Ifo+etoposide+Doxo); patient A2] followed by surgical removal of the remaining renal tissue.

In patients with DDS and unilateral WT, unilateral nephrectomy was followed by ‘prophylactic’ removal of the second kidney after 1–11 months. One patient with DDS (B2) underwent bilateral nephrectomy 6 months after presentation with nephrotic syndrome, hypertension and ESRF. She is the only patient in this series who did not have WT.

A minimum of 1 year tumour-free survival after completion of chemotherapy was a prerequisite to enter the transplantation programme. Four children received cadaveric kidneys and two received live-related allografts at a time interval ranging from 15 to 49 months after bilateral nephrectomy. All patients were maintained on renal replacement therapy, mainly continuous ambulatory peritoneal dialysis (CAPD), while awaiting renal transplantation. Four children also had short episodes of haemodialysis before or between periods of CAPD, and five children suffered at least one episode of dialysis-related peritonitis.

**Outcome**

One patient in this series (patient A1) died. An initial episode of acute rejection was followed by transient improvement of graft function, but renal function subsequently deteriorated. Despite treatment with pulsed methylprednisolone and a 10 day course of anti-thymocyte globulin therapy, the patient became ureaemic and needed haemodialysis 3 weeks after transplantation. Short-lived clinical improvement was followed by a haemolytic–uraemic syndrome. Therapy with plasma exchange was initiated, but the patient developed pulmonary oedema and died from untreatable congestive heart failure 5 weeks after his renal transplantation. Permission for post-mortem examination was refused.

For the other five children, mean follow-up post-renal transplantation is 59 (range 12–104) months. In one patient, the graft failed after 108 months, necessitating return to haemodialysis. The other four have remained clinically well and enjoy age-appropriate activities. Immunosuppression consists of prednisolone, cyclosporin A and azathioprine. One episode of acute rejection, associated with urinary candidiasis, occurred in one patient (B1), and two episodes of urinary tract infection in another (patient B2). Two children developed hypertension due to non-origin site renal artery stenosis (patients B3 and B4). The cause of this unusual complication remains unclear. Both were treated successfully with transluminal renal angioplasty. Stenosis recurred in patient B4 but did not require re-angioplasty. After renal transplantation, she also had two subsequent surgical re-examinations for urinary leakage. The latest assessments of renal function are summarized in the last column of Table 1.

In view of the risk of malignancy, gonadal excision was performed on patient B2 at 4 years post-transplant, and hormone replacement therapy (ethinyloestradiol) commenced at the age of 10 years.

**Discussion**

In a review of 185 patients with BWT registered with the National Wilms’ Tumour Study (NWTS) Groups II–IV, survival was 83, 73 and 70% at 2, 5 and 10 years, respectively. This excellent outcome may be the result of several factors, including an earlier age at which bilateral lesions are diagnosed, the high incidence of favourable histologic patterns and the excellent response of BWTs to chemotherapy. In this series, survival was not prejudiced by renal-sparing surgical procedures [8] but, in a small group of patients with BWT, complete surgical tumour removal may not be achievable without total bilateral nephrectomy. This was true in two patients with BWT, who relapsed soon after the first renal-sparing intervention, and therefore required removal of all remaining renal tissue.

The ‘common denominator’ of DDS is a nephropathy associated with genital abnormalities and/or WT. Nephropathy consists of varying degrees of diffuse or focal mesangial sclerosis with characteristic major involvement of the outer cortex. Early in life, most children develop proteinuria which usually evolves into nephrotic syndrome and eventually progresses to
ESRF. Seventy-six percent of 64 reported patients developed ESRF, 60% of them before the age of 2 years [5]. In the course of their disease, virtually all patients with DDS are destined to develop WT [10]. Six of the seven children in the series with DDS from this institution developed WT at <2 years of age (mean 1.6 years) [5], findings similar to those of Habib et al. in 10 children [11]. There is controversy as to whether patients with proven DDS require early bilateral nephrectomy in order to reduce the risk of WT, to avoid adverse effects of chemotherapy, including the prolongation of time to consideration for transplantation, and to reduce metabolic and nutritional sequelae of chronic renal failure. In patients with DDS, WT often develops prior to the onset of end-stage renal disease [4,5]. This observation, together with the favourable experience with renal replacement therapy and renal transplantation in these patients, endorses our view that it is preferable to proceed ‘early’ rather than ‘late’ in the course of the underlying renal disease.

A possible strategy for management may be derived from the treatment of these six patients. Diagnosis has to be established by appropriate imaging and renal biopsy. In the case of WT, the tumour size and the assessment of the oncologist and surgeon will determine whether it seems better to operate immediately or to prescribe chemotherapy. A course of pre-operative Vcr/Act-D chemotherapy may ‘downstage’ some WTs, and shrinkage of the tumour may improve operability and make a renal-sparing procedure possible. Post-operative chemotherapy and, in a few cases, radiotherapy, will depend on staging [12] and history of WT, 2 year disease-free survival after treatment is generally accepted as a measure of successful therapy, because the risk of later recurrence is extremely low [9]. As kidneys for donation are in short supply and children transplanted at intervals of less than 1 year after completion of chemotherapy are reported to have a high incidence of recurrence/metastases and infection [14,15], it seems reasonable to wait at least 1 year after completion of chemotherapy before considering renal transplantation. Careful, appropriate imaging investigations to exclude metastasis to lungs, liver, paraaortic lymph nodes and, in the case of unfavourable histology tumours, to bone and brain should precede enrolment in the renal transplant programme. Children free of evidence of tumour at this time may then be put on a waiting list for cadaveric transplantation, or a parental live-related transplantation might be considered. Imaging for recurrence of WT should continue for a total of 2 years from the end of all WT treatment, and can then be discontinued.

Advances in surgical techniques, chemotherapy, renal replacement therapy and transplantation programmes have enlarged the armamentarium available to cure patients with these two life-threatening conditions. The French series of Habib, who transplanted six of 14 DDS patients [16], and the report of the North American Pediatric Renal Transplant Cooperative Study, which includes 16 patients each with the diagnoses of BWT and DDS amongst a total of 3037 children who received 3286 renal allografts [17], endorse this view. Unfortunately, these reports do not provide any details about outcome.

Infections, hypertension, liver disease and an increased incidence of malignancy, especially lymphoproliferative disease (LPD), are well known causes of morbidity and mortality in renal transplant recipients. There is some concern that following chemotherapy for WT, patients might be placed at a higher risk than other children for some of these sequelae. In patient A1 (Table 1), who died within 5 weeks after renal transplantation, the dose-dependent cardiotoxicity of Doxo (total dose in our patient: 180 mg/m²) may well have contributed to the untreatable congestive heart failure and the fatal outcome. It is not yet clear whether chemotherapy prior to renal transplantation increases the incidence of post-transplant LPD.

Finally, as children with DDS survive through adolescence, the problems of male hermaphroditism and the potential risk of genital malignancy become a priority. Planned genital excision post-transplant and hormone replacement therapy are recommended.

In conclusion, our experience with renal transplantation in two patients with BWT and four with DDS is promising. Paediatric renal transplant centres should be aware of this relatively new indication for allogeneic renal transplantation. The complexity of these conditions and the special circumstances and needs of this group of patients demands a thoughtfully planned interdisciplinary approach and careful follow-up.

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**Appendix**

Current staging of Wilms’ tumour (National Wilms’ Tumor Study
III)*

Stage I
Tumour limited to kidney; complete excision. Capsular surface
intact; no tumour rupture; no residual tumour apparent beyond
margins of resection.

Stage II
Tumour extends beyond kidney but is completely excised.
Regional extension of tumour vessel infiltration; biopsy of
tumour performed or local spillage of tumour confined to the
flank. No residual tumour apparent at or beyond margins of
excision.

Stage III
Residual non-haematogenous tumour confined to the abdomen.
Lymph node involvement of hilus, periaortic chains, or beyond;
diffuse peritoneal contamination by tumour spillage or peritoneal
implants of tumour; tumour extends beyond surgical margins
either microscopically or macroscopically; tumour not completely
removable because of local infiltration into vital structures.

Stage IV
Deposits beyond stage III, i.e. lung, liver, bone, brain

Stage V
Bilateral renal involvement at diagnosis

*Data from ref. 13, by permission of Raven Press.

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