Congenital Nephrotic Syndrome: Preemptive Bilateral Nephrectomy and Dialysis Before Renal Transplantation

Melanie S. Kim, William Primack, and William E. Harmon

ABSTRACT
Congenital nephrotic syndrome (CNS) is a rare and uniformly fatal disease if it is not treated. Although renal transplantation has been a successful treatment, there remains a high mortality rate during the first year of life before transplantation. From 1979 to 1987, four patients with CNS, all of whom died before they could undergo renal transplantation were treated. On the basis of this clinical experience, early elective bilateral nephrectomy and dialysis for infants with CNS were initiated to improve overall outcome. From 1987 to 1989, this protocol has been used on four consecutive patients with CNS. In these patients, bilateral nephrectomy was performed only after patients suffered a serious CNS-related complication that occurred between 4 and 6 months of age. Despite nephrectomy and the need for chronic dialysis, all patients grew at normal or accelerated rates. By 16 months of age, all patients underwent successful renal transplantation.

Key Words: Nephrotic syndrome, infants, congenital nephrotic syndrome

Congenital nephrotic syndrome (CNS) manifests within the first 3 months of life and is distinct from childhood nephrosis because CNS is refractory to immunosuppressive therapy and is uniformly fatal if not treated (1,2). CNS is composed of a heterogeneous group of diseases that are defined by their renal histopathology (3,4). Infants with CNS, regardless of the underlying histopathology, have similar clinical courses consisting of failure to thrive, frequent serious infections leading to a mortality rate of 80% before 1 yr of age, and a decline in renal function in the few patients who survive the first year of life (1,2). These infants die as a result of complications of the nephrotic syndrome. Sepsis is the main cause of death in these patients whose risk of serious infection is greatly increased by anasarca and hypogammaglobulinemia (5).

Renal transplantation is the only effective treatment for CNS (2,6). The outcome of renal transplantation in infants, however, has often been poor (7–9). A major factor associated with this poor outcome is young donor age (8,10,11). Thus, some programs have suggested that transplantation be delayed until the infant is large enough to receive a graft from an adult donor (9,12). In general, infants with chronic renal insufficiency may reach the size necessary to receive an adult kidney (about 65 cm in length or 6.5 kg in weight) by about 1 yr of age. Substantial mortality occurs, however, in infants with CNS during the first year of life (2,6) before a size appropriate for renal transplantation from an adult donor is achieved.

Elective bilateral nephrectomy has been recommended for infants with CNS to alleviate risk factors associated with the nephrotic state and to allow affected infants to grow before transplantation (13). Early nephrectomy would be reasonable as long as it would diminish the first-year mortality and also permit sufficient growth in these infants. Current trends in the treatment of children who receive renal transplants can be obtained from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). NAPRTCS was organized in 1987 and comprises the majority of centers that perform renal transplants in children less than 18 yr of age. Between 1987 and 1990, 63 centers registered 1,667 renal transplants with NAPRTCS. Of these, 43 were in patients with CNS. Only 22 of the 43 patients had bilateral nephrectomy performed before transplantation (NAPRTCS, personal communication). Furthermore, it should be noted that the NAPRTCS data

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include only those patients who have been transplanted. There is no information available on the number of infants with CNS who may have died before transplantation was attempted. Thus, it appears that a large number of pediatric transplant programs do not follow this recommendation for pretransplant bilateral nephrectomy.

We reviewed, therefore, the result of the treatment of infants with CNS at Children’s Hospital to determine what effect early elective bilateral nephrectomy had on the overall outcome.

METHODS

Serum IgG and albumin were measured by serum immunofixation electrophoresis. Serum creatinine values were measured by the Ektachem® (Kodak, Rochester, NY) method in the clinical chemistry lab of the Children’s Hospital.

Renal biopsy and nephrectomy specimens were available from all patients. Light microscopy specimens were fixed in Bouin’s solution, and sections were cut at 2 to 3 microns. Sections were stained with hematoxylin and eosin, periodic acid-Schiff, Masson trichrome, Jones’ silver methenamine. Tissue for electron microscopy was embedded in Epon with primary fixation with Karnovsky’s fixative. Frozen sections from specimens were stained with fluorescence-labeled antibodies to human IgG, IgM, IgA, C3, C4, fibrin, and albumin.

Length was measured at monthly intervals by standard methods, and linear growth velocity rates were calculated by linear regression for each patient during the period of time that he or she was being treated with dialysis; these rates were compared with standard values (14).

RESULTS

Between 1980 and 1989, eight consecutive infants with primary CNS were seen at Children’s Hospital. All patients had edema, hypalbuminemia, hyperlipidemia, and severe proteinuria. Before 1987, four patients with CNS were treated medically with a high-calorie, high-protein, and low-salt diet. Intravenous albumin and diuretics and parenteral antibiotics were used as clinically indicated. Despite these efforts, all patients died from sepsis. Death occurred at 7, 8, 9, and 16 months of age.

From 1987 to 1989, four infants were treated initially as described above but early bilateral nephrectomy was performed between 4 and 6 months. Each patient’s parents had agreed that bilateral nephrectomy and the initiation of dialysis would be undertaken only after the patient had a serious complication. These complications included life-threatening infection, failure to thrive (defined as linear growth velocity that was less than 2 SD below the third percentile), intractable edema (defined as prolonged inpatient hospitalization for repeated iv infusions of albumin and diuretics), or a severe thrombotic event (thrombosis of a major blood vessel or organ).

Clinical features, family history, and laboratory data of the four patients are shown in Table 1. Patients 1 and 2 were brothers whose two previously affected siblings had died from CNS. Patient 3 was initially detected by an elevated amniotic fluid α-fetoprotein level. Each of these three patients was born prematurely, had a large placenta, and had

TABLE 1. Clinical features of patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Family History</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gestational Age (wk)</td>
<td>36</td>
<td>35</td>
<td>36</td>
<td>40</td>
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<tr>
<td>Placentomegaly</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA*</td>
</tr>
<tr>
<td>Increased AFP*</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>At Presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Albumin (g/dL)*</td>
<td>0.9</td>
<td>1.0</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>UA Protein*</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>Serum IgG (g/dL)*</td>
<td>175</td>
<td>&lt;42</td>
<td>&lt;42</td>
<td>83</td>
</tr>
<tr>
<td>At Nephrectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Indication</td>
<td>Sepsis</td>
<td>Arterial thrombosis</td>
<td>Sepsis</td>
<td>Edema, failure to thrive</td>
</tr>
</tbody>
</table>

* NA, information not available.

* Amniotic α-fetoprotein.

* Normal value, 3.5 to 5.5 g/dL.

* Protein determination by urinalysis (UA) dipstick.

* Normal value, 639 to 1,344 mg/dL.
laboratory findings consistent with nephrosis at birth. Patient 4 presented at 2 months of life with a right inguinal hernia. An evaluation revealed abdominal ascites, low serum albumin, proteinuria, hyperlipidemia, and a low IgG level. VDRL and TORCH titers were negative.

The pathologic findings from all four patients were consistent with CNS of the infantile microcystic type (3). Each specimen exhibited immature or microcystic glomeruli and cystically dilated proximal tubules, particularly in juxtamedullary nephrons with variable degrees of segmental and global sclerosis. Immunofluorescence was unremarkable. Electron microscopy uniformly displayed diffuse foot process fusion.

By 6 months of age, each patient had a serious complication directly attributable to the chronic nephrotic state. Table 1 lists the complications that led to nephrectomy, the serum creatinine values, and the age of each patient at the time of nephrectomy. Patients 1 and 3 had culture-proven sepsis with Klebsiella pneumoniae and Bacteroides fragilis. Patient 2 had arterial vascular occlusion of the right dorsalis pedis artery, the right posterior tibial artery, and the right radial and right ulnar arteries. Patient 4 had failure to thrive and intractable edema.

After bilateral nephrectomy, peritoneal dialysis was initiated in all four patients (Table 2). Three patients were treated with continuous cycling peritoneal dialysis with a prescription of six to seven exchanges (40 mL/kg) every 2 h overnight. Patient 3 received continuous ambulatory peritoneal dialysis with a prescription of five exchanges (30 mL/kg) over 24 h. Glucose concentration for either method of dialysis varied, depending on the patients’ weights and fluid status. Patients were maintained on a high-calorie diet designed to minimize urea generation (9.7 kcal/cm of height) (15). Feedings were administered by the nasogastric route in three of four patients. All patients received NaCl supplementation, vitamin D either as dihydrotachysterol or 1,25-dihydroxy-cholecalciferol, and folic acid. Calcium supplementation was given to three of the patients, and only patient 1 required aluminum hydroxide as a phosphate binder. There was no radiologic evidence of osteodystrophy in any of the patients.

During dialysis, patients 1 and 2 experienced no complications. Patient 3 had an episode of hypernatremia at 7 months of life, secondary to an improperly prepared dialysate solution. In addition, he underwent correction of bilateral inguinal hernias at 11 months of age. Patient 4 had eosinophilic peritonitis, and at 6 months of age, leakage at the catheter site required a catheter change. At 9 months of age, she developed Pseudomonas aeruginosa peritonitis that was refractory to antibiotic therapy. Chronic hemodialysis was initiated and maintained until she received a renal transplant at 13 months of age.

Growth data during dialysis are summarized in Table 2. Three of the patients had normal growth velocity for age, and the other patient displayed accelerated growth. By 16 months, all patients had grown to sufficient size to undergo transplantation. Patient 1 received a cadaveric renal allograft, and the other three patients received grafts from a parent. Patient 4 died 13 months after renal transplantation from vasculitis of unknown causes. The other three patients have functioning grafts 27 to 40 months after transplantation.

**DISCUSSION**

Previous reports have shown that renal transplantation is an effective therapy for CNS (2,6). However, there remains a high rate of mortality during the first year of life while the patient is awaiting transplantation. In 1984, Mahan et al. reported a 25% mortality rate among patients with CNS who were awaiting

**TABLE 2. Clinical features of patients during dialysis**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (months)</th>
<th>Dialysis Modality</th>
<th>Daily Intake Calories (cal/cm)</th>
<th>Protein (g/cm)</th>
<th>NGT</th>
<th>BUN (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Duration (months)</th>
<th>Growth Velocity (cm/yr)</th>
<th>Height (cm)</th>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>CCPD</td>
<td>9.4</td>
<td>0.22</td>
<td>Yes</td>
<td>20</td>
<td>3.2</td>
<td>12</td>
<td>16.6</td>
<td>70.0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>CCPD</td>
<td>9.7</td>
<td>0.12</td>
<td>Yes</td>
<td>21</td>
<td>5.5</td>
<td>7</td>
<td>26.4</td>
<td>70.5</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>CAPD</td>
<td>10.5</td>
<td>0.40</td>
<td>No</td>
<td>27</td>
<td>4.4</td>
<td>8</td>
<td>13.7</td>
<td>70.5</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>CCPD HD</td>
<td>10.5</td>
<td>0.28</td>
<td>Yes</td>
<td>35, 22</td>
<td>5.0, 5.2</td>
<td>8</td>
<td>11.5</td>
<td>69.0</td>
</tr>
</tbody>
</table>

Age at initiation of dialysis.

Method of dialysis: CCPD, continuous cyclic peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis.

Nasogastric tube feeding.

Average value while on dialysis.

Duration of treatment with dialysis.

Normal growth velocity for boys at 10.4 months 14.5 ± 4.25 cm/yr; normal growth velocity for girls at 10.4 months 15.9 ± 4.25 cm/yr.

Height at time of renal transplantation.
transplantation (2). In that report, four patients died from infection and two were reported to have died from central nervous system deterioration. In 1990, Holmberg et al. reported a mortality rate of at least 17.5% in the first year of life (6). The mean age of nephrectomy or initiation of dialysis in patients from these two reports who were subsequently transplanted was 40 months (2) and 17 months (16) and the mean age at time of first transplantation was 43 months (2) and 27 months (6). At these centers, the main indication for preemptive nephrectomy was poor growth. Furthermore, in 1987, Mahan and Vernier recommended that infants with CNS should have nephrectomy and short-term dialysis at the time of planned renal transplantation in order to achieve an anabolic state by eliminating protein loss and to eliminate the hypercoagulable state associated with the nephrotic syndrome (13). Despite these recommendations, it appears that up to one half of the children with CNS do not have bilateral nephrectomy performed before renal transplantation.

With the history of poor outcome of infants with CNS before 1987 at our center and with the improvements in chronic dialysis treatment for infants, the indications for preemptive nephrectomy were expanded to include not only poor growth but other serious complications attributable to the nephrotic state, such as a single life-threatening infection, a severe thrombotic event, or intractable edema. By these criteria, four patients with CNS who presented between 1987 and 1989 underwent bilateral nephrectomy between 4 and 6 months of age. Patients were maintained on chronic dialysis from 7 to 12 months. All patients grew well on dialysis with growth velocity between 11.5 to 26.4 cm/year. All patients received renal transplants by 16 months of age.

This study confirms the observation that the removal of the affected kidneys in infants with CNS despite normal GFR eliminates protein losses and results in excellent growth. All four patients who underwent early nephrectomy not only survived the first year of life but thrived and grew at a rate that enabled them to achieve sufficient size to receive an adult renal allograft by 16 months of age. These results support the recommendations set forth by Mahan and Vernier that all patients with CNS should have nephrectomy performed before renal transplantation. Furthermore, because chronic dialysis can be successfully performed at a very early age (16,17), nephrectomy should be considered early in the course of the disease and the indications for nephrectomy should not only include poor growth but also other serious complications of the nephrotic state such as sepsis, thrombosis, and intractable edema.

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REFERENCES