Recurrence of Primary Renal Disease on Kidney Graft: A European Pediatric Experience

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ABSTRACT
Of the 4,776 first grafts recorded in the pediatric European Dialysis and Transplant Association (EDTA) registry, 2,113 were reported to have failed and 5.6% of graft failures were related to a recurrence of primary renal disease. Nephrotic syndrome with focal and segmental glomerulosclerosis was the main renal disease prone to recur because recurrence represented 20% of the causes of graft failure in these patients; an even higher proportion was reported in a single-center experience in Europe. Other glomerulonephropathies, such as membranoproliferative glomerulonephritis and Berger's disease, were also reported to be the cause of graft failure by means of recurrence in a proportion similar to focal and segmental glomerulosclerosis. The usual recurrence of primary oxaluria was the cause of close to 50% of graft failure in this disease. Finally, hemolytic uremic syndrome occurred rarely with the graft in the EDTA registry, which is the opposite of what was reported in the United States.

Key Words: kidney transplantation, children, focal segmental glomerulosclerosis, recurrence (on the graft)

Recurrence of primary renal disease (PRD) may represent a more important cause of graft failure in children than in adults, because the diseases known to be able to recur, such as focal segmental glomerulosclerosis (FSGS) or oxalosis, are a relatively more frequent cause of end-stage renal disease in children than in adult patients. The purpose of the study was to give some data from the European Dialysis and Transplant Association (EDTA) registry on this subject.

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METHODS
Analyses were performed through the database of the EDTA Paediatric Registry, made up of patients of ages less than 15 yr at the start of renal replacement therapy. The treatment of individual patients has been reported to this registry and computerized since 1970. The essential structure of the patient questionnaire, which is updated each year, has remained the same since 1971. The first part of the form consists of patient identification data, including the primary renal disease causing end-stage renal failure. "Glomerulonephritis," hemolytic uremic syndrome, and oxalosis were reported from the beginning, FSGS was added in 1980, dense-deposit disease was added in 1984, Immunoglobulin A nephropathy (proven by immunofluorescence not Schoelein-Henoch) was added in 1985, and membranous glomerulonephritis was added in 1986.

This part also includes the time sequence recording the dates of commencement of each method of treatment. The second part of the form contains questions relating to each particular mode of therapy, including the cause of graft failure. There were nine possible codes reportable since 1971:

- code 1—hyperacute rejection,
- code 2—rejection,
- code 3—rejection without taking medication,
- code 4—recurrence of PRD,
- code 5—vascular or ureteric postoperative problem,
- code 6—vascular thrombosis not related to operation,
- code 7—infecction of graft,
- code 8—removal of a functioning graft, and
- code 9—nonviable kidney.

The registry mails yearly to each center a batch of questionnaires, which are returned to the registry after updating. Collaboration with the transplant registries Euro-Transplant, France-Transplant, and the U.K. Transplant Service helped to provide more comprehensive data concerning transplantation. Only first grafts that had been documented between 1970 and December 1989 were considered in this study.

RESULTS
Causes of Graft Failure
A total of 4,776 first grafts were recorded in the pediatric registry from 1970 to 1989, but 264 were
not updated and were considered as lost to follow-up. During this period of time, 2,113 of these grafts were reported to have failed. Unfortunately, the cause of graft failure was only given for 1,674 patients (Table 1): 76.9% of failure was reported to be related to rejection, 12.3% to vascular or ureteric problems, 5.6% to recurrence of PRD, 1.7% to infection, 1% to the removal of a functioning graft, and 2.2% to a nonviable kidney.

Failure Related to Recurrence

Analyzing the PRD in graft failures that were reported as being related to recurrence, it was found that 22 of these reports were erroneous because the PRD of these patients were not really prone to recur (congenital hypoplasia/dysplasia of the kidney, pyelonephritis, hereditary disease not specified, nephronphthisis, traumatic loss of the kidney, cortical necrosis, reflux, and in four cases, the PRD was not given or was reported as "other"). Finally, there were only 73 reported graft failures due to recurrence of a disease known to be able to recur (Table 2), that is to say, 4.3% of reported failures.

The majority of these cases were reported with the primary diagnosis of glomerulonephritis type unspecified; this group of patients probably included a number of cases of nephrotic syndrome with FSGS, which is the main identified disease with a risk of recurrence on the graft.

Nephrotic Syndrome With FSGS

Three hundred thirty first grafts were reported in pediatric patients whose PRD was nephrotic syndrome with FSGS. At the time of analysis, 154 of these grafts had failed, but the cause of graft failure was known in only 120 cases: 72 (60%) were related to rejection; 24 (20%) were related to recurrence; and, among other causes, 13 (10%) were due to vascular thrombosis not related to operative problems.

IgA Mesangial Deposit (Berger’s Disease)

Twenty nine first grafts were reported in pediatric patients whose PRD was Berger’s disease. At the time of analysis, 12 of these grafts had failed but the cause of graft failure was known in only 10 patients: 2 of them lost the graft because of recurrence and 8 lost the graft because of rejection.

Dense-Deposit Disease (Mesangioproliferative Glomerulonephritis Type II)

Twenty seven first grafts were reported in pediatric patients whose PRD was recorded as dense-deposit disease. Ten grafts failed, and the cause of failure was reported in seven. Two of these failures were related to recurrence.

Hemolytic Uremic Syndrome

One hundred seventy first grafts were reported in pediatric patients whose PRD was recorded as HUS. Seventy-five of these grafts failed, and the cause of graft failure was reported in 45; 38 were related to rejection, and only 1 (2.2%) was related to recurrence.

Oxalosis (Primary Hyperoxaluria)

Thirty six first grafts were reported in pediatric patients whose PRD was recorded as oxalosis. Twenty-two of these grafts failed, and the cause of graft failure was reported in 18; 8 (46%) were related to recurrence.

Miscellaneous

It is noteworthy that out of 11 first grafts in patients whose PRD was membranous glomerulonephritis, there were 4 graft failures but none due to recurrence. The same was found in the group of renal

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<table>
<thead>
<tr>
<th>Causes</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute Rejection</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Rejection</td>
<td>1,585</td>
<td>76.9</td>
</tr>
<tr>
<td>Rejection without Taking Medication</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Recurrence of PRD</td>
<td>95</td>
<td>5.6</td>
</tr>
<tr>
<td>Vascular or Ureteric Postoperative</td>
<td>111</td>
<td>12.3</td>
</tr>
<tr>
<td>Problem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular Thrombosis Not Related to</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection of Graft</td>
<td>29</td>
<td>1.7</td>
</tr>
<tr>
<td>Removal of a Functioning Graft</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Nonviable Kidney</td>
<td>38</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Total number of graft with update, 4,512; total number of graft failures reported, 2,113; recorded cause of failure, 1,674.

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**TABLE 2. PRD in cases of first graft failure to recurrence in the EDTA Pediatric Registry**

<table>
<thead>
<tr>
<th>PRD</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis (Type Not Specified)</td>
<td>35</td>
</tr>
<tr>
<td>Nephritic Syndrome with FSGS</td>
<td>24</td>
</tr>
<tr>
<td>Oxalosis</td>
<td>8</td>
</tr>
<tr>
<td>IgA Mesangial Deposits Disease</td>
<td>2</td>
</tr>
<tr>
<td>Schoenlein-Henoch</td>
<td>2</td>
</tr>
<tr>
<td>Hemolytic Uremic Syndrome</td>
<td>2</td>
</tr>
</tbody>
</table>
vascular diseases (polyarteritis, Wegener’s granulomatosis, malignant hypertension). Thirty one graft failures were reported in 59 first grafts performed in this group of patients, but none were due to recurrence. Finally, out of the 10 graft failures recorded in 25 patients with Wilms’ tumor, none were caused by recurrence.

DISCUSSION

The information revealed by this study raises several questions inherent to any multicenter international database. The first possible bias was the number of grafts lost to follow-up. These were 264 at the time of analysis, that is to say, 5% of reported grafts. This is a relatively small proportion, not likely to create a bias. The proportion of graft failures recorded without a cause was much higher: 439 out of 2,113 or to say 20%, and this is a matter of uncertainty for this study even if there is no reason to think that any cause of graft failure could be more frequent in the nonreported group. The most important criticism, however, comes from the PRD definitions. As mentioned in the Methods section, all kidney diseases were given a code at the commencement of the registry in 1970. Because of the difficulties in finding a general agreement on the pathological definitions, glomerulonephritis was recorded without further subdivision until recently. Between 1980 and 1986, FSGS, Berger’s disease, dense-deposit disease, and membranous glomerulonephritis were separately identified. Therefore, only a limited number of cases of some diseases were available for this study, limiting its validity. Finally, because of inadequate reporting in patients who died with a graft without returning to dialysis, it is difficult to be sure how many of these had in fact suffered graft failure.

With all of these reservations in mind, a proportion of 4.3% of graft failure was reported to have been caused by the recurrence of PRD in the pediatric EDTA registry. This figure is similar to the proportion reported in the Canadian registry in 1987 (3 of 91, i.e., 3.3%) (personal communication) and in the North American cooperative transplant program in 1989 (7 of 154, i.e., 5%).

Interestingly, graft loss due to recurrence was a more important cause of graft failure in several single-center pediatric reports. For example, this cause represented 13% of graft failures in the Enfants Malades Hospital in Paris (1).

Nephrotic syndrome with FSGS is the main renal disease prone to recur in the graft. As a matter of fact, recurrence represented 20% of causes of graft failure in this study. Because of the number of records that were not updated, it was not possible to give the actual proportion of first grafts lost to recurrence, which could only be estimated as about 8% in this series (24 of 296). A higher proportion was reported in two important European pediatric transplant series: 19% in the Enfants Malades series (1) and 37% in the Guy’s Hospital pediatric series (2). The higher proportion reported in the single-center experiences could be in relation to a more precise definition of PRD. Several other diseases such as diffuse mesangial sclerosis or other familiar glomerular diseases that do not recur in the graft could have been considered as FSGS in some other centers, falsely increasing the denominator.

The small number of cases does not really permit estimation of graft loss due to recurrence in Berger’s disease or in dense-deposit disease. This proportion nevertheless represented 20 and 28%, respectively, that is to say figures similar to those noted for FSGS.

Primary hyperoxaluria is known to be associated with a high risk of recurrence (3). This risk is again pointed out in this series, with 40% of graft loss to recurrence.

Hemolytic uremic syndrome rarely recurred on the graft in the present study, because only 2 out of 71 failures were recorded as due to recurrence. This small proportion is at variance with what was reported by the Minneapolis group which found a proportion of 25% graft loss to recurrence (5). This difference raises unsolved questions.

REFERENCES