Predictive value of race in post-transplantation recurrence of focal segmental glomerulosclerosis in children

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Abstract

Background. Focal segmental glomerulosclerosis (FSGS) is a leading cause of end-stage renal disease (ESRD) in children, and one of the most difficult to manage because of its high recurrence rate post-transplantation (Tx). Several predictive factors have been associated with disease recurrence (DR) although one in particular, the role of recipient race, has not been adequately evaluated. Herein we report our experience with DR in the post-Tx period in eight patients.

Methods. Records were reviewed for all renal transplants performed at St Christopher’s Hospital for Children from 1971 to 1997.

Results. Twenty patients received 27 allografts for ESRD due to FSGS. Ten (37%) grafts went to African-American (AA) children, and 16 (59%) to those of Caucasian (C) origin. DR was observed in eight (30%) grafts after Tx. No differences were noted between the patients who developed DR and those who did not, with respect to age at diagnosis or time to ESRD. DR was observed in one (10%) of 10 grafts in AA, compared to seven (41%) of 17 grafts in the other (O) racial groups (P=0.19). At last follow-up, the only AA recipient with DR has maintained stable renal function, while three (43%) of seven in O have lost their grafts.

Conclusion. In conclusion, in our population post-Tx recurrence of FSGS occurred more frequently and represented a greater threat to graft survival in O recipients than in those of AA descent. Recipient race should therefore be taken into consideration during pre-Tx counselling of families of children with FSGS.

Key words: FSGS; nephrotic syndrome; race; recurrence; transplantation

Introduction

FSGS is a distinct histopathological entity [1] that frequently presents as corticosteroid-resistant nephrotic syndrome in children, approximately one-third of whom progress to ESRD [2]. In a substantial proportion, FSGS recurs following Tx, resulting in graft loss in about one-half [3–7]. Predictive factors that have been associated with a high risk of DR are a younger age at presentation [6–8], progression to ESRD within 3 years of disease onset [6,8], and in some reports the identification of mesangial proliferation on native kidney biopsy [3,6,8,9]. The predictive role of recipient race in recurrence of FSGS has been inadequately addressed. To date, this issue has been investigated in only one report, in which a reduced risk of DR was demonstrated in AA [9].

Subjects and methods

Records were reviewed for all renal transplants performed at St Christopher’s Hospital for Children from 1971 to 1997. Children whose native kidney biopsy showed clear evidence of FSGS were identified, and their charts reviewed to obtain demographic information and data relating to their post-Tx clinical course. Patients with a histological diagnosis of FSGS who presented with ESRD, but without a preceding history of clinical nephrosis, were excluded from the analysis. DR was defined as the appearance of nephrotic-range proteinuria (>40 mg/h/m²) in the absence of acute or chronic rejection, and was confirmed by allograft biopsy. Fisher’s two-tailed exact test was used for statistical analysis of differences between the cohort of patients with and without DR.

Results

From January 1971 to June 1997, 367 renal transplants were performed in 269 children at St Christopher’s Hospital for Children. Of these, 27 were for ESRD due to primary FSGS in 20 patients. At the time of Tx, these 20 patients had a mean age of 12.5 (range 3.3–18.6) years. There were 11 (55%) males; 12 (60%) were C, seven (40%) were AA and one (4%) was Oriental. The mean age at diagnosis of FSGS was 5.8 (range 0.3–13.7) years, and the mean interval from disease onset to ESRD, the latter defined as the time of initiation of dialysis or of renal Tx, was 5.9 (range 0.3–13.7) years. Since the diagnosis of FSGS was not...
made by renal biopsy performed at St Christopher’s Hospital for Children in all cases, and information regarding the degree of mesangial proliferation was not available in a number of the outside reports, this information was not included in our analysis. Of the 27 allografts, six (22%) were from living related (LR), and 21 (78%), were from cadaveric (CR) donors. Clinical evidence of DR was observed in eight (30%) grafts, at a mean interval of 194 (range 1–1369) days following Tx.

In seven patients, the disease recurred immediately post-Tx, at a mean interval of 9 days. The only patient with a late recurrence of FSGS had continued to experience nephrotic-range proteinuria while receiving dialysis during the pre-Tx period. Post-Tx, his proteinuria decreased to 450 mg/day, but subsequently began increasing and reached a maximum of 9.7 g/day, 3.5 years later. A trial of oral corticosteroids and cyclophosphamide failed to arrest disease progression, and his graft was lost over the ensuing 2 years.

For the eight patients with DR, the mean duration of follow up after Tx was 7.9 (range 0.3–16.8) years. At last follow-up, five (63%) allografts were functioning without problems, while three had been lost; two in the immediate post-Tx period to acute rejection, and one to chronic rejection 6 years later, after having experienced multiple episodes of corticosteroid-resistant acute rejection. Of the five patients with functioning allografts, one had received a 3-day course of intravenous albumin and frusemide, another had received three daily doses of intravenous methylprednisolone for acute rejection, and a third had received nine treatments of plasmapheresis and 12 weeks of oral cyclophosphamide. When patients with and without DR were compared, there were no significant differences between the two groups with respect to gender, mean age at onset of FSGS, mean age at Tx, or mean time to progression to ESRD (Table 1). DR was more commonly observed in the O racial group (7 of 17 patients (41%), than the AA group (1 of 10 patients (10%) (P=0.19), and also in grafts from LR donors (4 of 6 (67%), compared to those from CR donors (4 of 21 (19%)) (P=0.04).

The only AA patient with DR continues, at last follow-up, to have stable renal function despite with a progressive deterioration in renal function, is surprising in view of previous observations that most nephrotic-range proteinuria, whereas three grafts in the O group have been lost. When the data were analysed separately for the two racial groups, no differences were noted in the incidence of DR with respect to donor source (0/9 CR donor allografts in the AA cohort had DR vs 1/1 CR donor allograft in the O group (P=0.10)). On the other hand, when analysed separately by donor source, although there were no differences in DR among the two racial groups for LR donor allografts, a higher risk of DR was found in recipients of CR donor allografts in the O racial group (0/9 in the AA group vs 8/12 in the O group (P=0.004)).

Discussion

FSGS is among the four leading causes of ESRD in the paediatric population and accounts for 11.8% of all transplants recorded in the North American Pediatric Renal Transplant Cooperative Study registry [10]. The disease has been reported to recur in about 10–50% of grafts after Tx, and is associated with a substantial risk of graft failure [11]. The pathophysiology underlying the recurrence of FSGS is unclear, although the process is considered to be mediated by a disturbance in immune regulation. A circulating protein factor shown to increase glomerular permeability to albumin has recently been identified in the sera of some patients with DR [12]. Factors felt to be predictive of DR include age under 13 years at presentation, and rapid progression to ESRD; some centres have also reported an association between DR and the presence of mesangial proliferation on native kidney biopsy. Our experience suggests furthermore that race is an additional important predictive factor.

The small sample size of our study does not permit the use of multivariate analysis to determine which of the two variables (donor allograft source and recipient race) have an independent impact on the risk of DR, although the statistically significant higher risk of DR observed in our O racial group, who received allografts from CR donors, points towards the potential importance of recipient race in recurrence of FSGS post-Tx.

The higher recurrence rate seen among C (who made up most of the O group), especially that associated with a progressive deterioration in renal function, is surprising in view of previous observations that most kidney diseases, including FSGS, appear to be more common among AA, in whom a more rapid rate of progression to ESRD has also been observed [13].

The higher rate of DR observed by us among recipients of LR donor grafts, attributed to better HLA matching [14], or alternatively to a genetic diathesis, has been previously reported, both for FSGS and for other primary glomerulonephritides [15]. Furthermore, once an allograft fails because of DR, the risk of recurrence increases substantially for subsequent allografts [3,6].

In view of these observations, several centres, including our own, have advocated using allografts from CR donors at the time of the initial transplant, reserving LR donor kidneys for subsequent transplants in case

Table 1. Recurrence of FSGS after renal transplantation

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<tr>
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<th>DR (n=8)</th>
<th>No DR (n=19)</th>
<th>P</th>
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<tr>
<td>Age at onset of NS (years)</td>
<td>6.4</td>
<td>5.4</td>
<td>NS</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>50</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Race (AA:O)</td>
<td>0.004</td>
<td></td>
<td></td>
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<tr>
<td>Donor (% LR)</td>
<td>50</td>
<td>11</td>
<td>0.04†</td>
</tr>
<tr>
<td>Age at Tx (years)</td>
<td>10.9</td>
<td>13.2</td>
<td>NS</td>
</tr>
<tr>
<td>Time to ESRD (years)</td>
<td>3.8</td>
<td>6.9</td>
<td>NS</td>
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<td>NS, not significant; *marginally significant; †significant.</td>
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the first allograft fails due to causes other than DR. It is therefore important to realize that, as a policy, our centre has discouraged the use of LR donor grafts for FSGS. Consequently the data in this regard pertain to a very select population of patients and are subject to selection bias. Larger studies are needed to better evaluate this risk, since it may play a very important role in pre-Tx planning, particularly in the selection of immunosuppressive therapy and counseling of families about possible outcomes.

References


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