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Single-center analysis of early recurrence of nephrotic syndrome following renal transplantation in children

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Abstract

Recurrence of nephrotic syndrome (NS) after transplantation (Tx) occurs in 20–50% of renal transplant recipients, with a median time to recurrence of 14 days and a 50% rate of graft loss. We performed a retrospective analysis of 22 pediatric patients with NS who received renal transplants at the Children's Hospital, Boston, between 1982 and 1999. During the first 14 days following Tx, 13 (59%) patients developed clinical recurrent nephrotic syndrome (RNS). RNS developed in 50% of living donor recipients and in 70% of cadaveric donor recipients ($p = \text{non-significant}$). Seven of the 13 patients with RNS were treated with plasmapheresis, while six received standard immunosuppressive induction therapy only. Two of the seven treated patients and one of the six untreated patients lost their grafts to RNS, yielding a total RNS graft loss rate of 23%. However, patients with RNS who achieved remission had significantly higher cumulative graft survival at 5 yr than did RNS patients who did not achieve remission ($p < 0.001$). Overall cumulative graft survival at 5 yr was not significantly different between the two groups: 67% in those with non-recurrent nephrotic syndrome (NRNS) vs. 64% in those with RNS, $p = \text{non-significant}$. We conclude that successful reversal of early RNS improves long-term graft survival in pediatric RNS. Multi-center studies are sorely needed to develop novel, less toxic therapies for native and recurrent NS.

Keywords

focal glomerulosclerosis; nephrotic syndrome; kidney transplantation; recurrence; plasmapheresis; graft survival; pediatrics

Abbreviations

NRNS, non-recurrent nephrotic syndrome; NS, nephrotic syndrome; RNS, recurrent nephrotic syndrome; Tx, transplantation

Focal segmental glomerulosclerosis (NS) is the most common glomerular disease causing renal failure in children (1). Recurrence of NS following Tx occurs in up to 50% of patients (2–4) and is associated with a 50% risk of renal allograft loss (5,6). The median time to recurrence is 14 days after Tx (4), suggesting a role for a circulating plasma factor present at the time of Tx.

Plasmapheresis or protein A adsorption has been used with some success to treat both native NS (7) and early RNS after Tx (5,8–12). In addition, the use of prophylactic plasmapheresis

has been proposed for patients with identifiable risk factors for RNS (13). Several groups have investigated the role of a circulating factor or group of factors in RNS (14–18). Although the true nature of this factor remains elusive, several inhibitors have been demonstrated *in vitro* (ref. 17; V. J. Savin, personal communication).

We performed a retrospective single-center analysis of the impact of successful reversal of early RNS on long-term graft survival, in order to determine whether multi-center investigative and therapeutic studies are warranted.

Materials and methods

A manual search of all transplant records and flow-sheets within the Renal Dialysis and Transplantation Program at the Children's Hospital, Boston, revealed a total of 22 patients with biopsy-proven (native kidney) NS who underwent renal Tx at this institution between 1982 and 1999. Any missing laboratory or clinical information was obtained from the hospital's internal server database. Information collected included: patient demographics; transplant number (index vs. repeat); pretransplant nephrectomy; donor source; warm ischemic times; induction therapy; additional therapy for RNS (plasma-pheresis, cyclophosphamide); blood chemistries (creatinine, albumin) during the first two post-transplant weeks; urine indices (protein, creatinine) during the first two post-transplant weeks; renal pathology; and the most recent clinical information pertaining to renal status.

Early recurrence was defined as either nephrotic-range proteinuria, i.e. a spot urine protein-to-creatinine ratio (mg/dL:mg/dL) of ≥ 3 , or a serum albumin level of 2.5 g/dL or lower, during the first 14 days following renal Tx. Patients demonstrating either of these criteria were classified as having RNS and those demonstrating neither criteria were classified as having non-recurrent NS (NRNS). Although diagnostic renal biopsies were performed and demonstrated extensive podocyte fusion in RNS, pathologic criteria were not used because the early and abrupt nature of the recurrence probably negated any diagnostic benefit in the first 14 days following Tx. Remission was defined as sustained non-nephrotic proteinuria and normalization of serum albumin. Primary non-function was defined as the need for dialysis within the first week following Tx or as the absence of a decrease in serum creatinine during the first 2 weeks after Tx. Graft loss was defined as the initiation of chronic dialysis or re-Tx.

Discrete data were compared utilizing the chi-square test. Continuous data were compared using the two-tailed unpaired *t*-test for normally distributed data and by the Mann–Whitney test for non-parametric data. Kaplan–Meier graft survival curves were generated and analyzed by the Cox proportional hazards ratio. Values are expressed as mean $\pm$ SD. Two-tailed *p*-values of ≤ 0.05 were considered statistically significant.

The Protection of Human Subjects was maintained in accordance with Title 45 CFR 46.101 (b) (4).

Results

Analyses for baseline differences between RNS and NRNS revealed that patients with RNS underwent renal Tx at a significantly younger age (RNS 9.5 ± 4.1 yr vs. NRNS 16.2 ± 4.9 yr, $p = 0.002$). Otherwise, the two groups were not significantly different with respect to the use of antibody induction therapy, incidence of repeat Tx, donor source, or warm ischemic times. Moreover, the incidence of primary non-function was not significantly different between the two groups (RNS 30% vs. NRNS 22%). However, there was a slight trend towards primary nonfunction in the RNS group.

During the first 14 days following Tx, 13 (59%) patients developed RNS. Nine of 14 (64%) index transplant recipients developed RNS and four of eight (50%) repeat transplant recipients developed RNS ($p = \text{non-significant}$). RNS developed in six of 12 (50%) living donor recipients and in seven of 10 (70%) cadaveric donor recipients ($p = \text{non-significant}$). RNS developed in 56% of patients who had undergone pretransplant native nephrectomies and in 60% of patients who retained their native kidneys at the time of transplant ($p = \text{non-significant}$). Within the RNS group, 75% of those who achieved remission had undergone pretransplant native nephrectomies and 75% of those who did not achieve remission had also undergone pretransplant native nephrectomies.

Seven of the 13 patients with RNS were treated with plasmapheresis, while six received standard immunosuppressive induction therapy only. Two of the seven patients treated with plasmapheresis also received daily oral cyclophosphamide therapy. Both patients received cyclophosphamide at a dosage of 2 mg/kg daily. One patient received cyclophosphamide for 52 days (post-transplant days 31–82), while the other received cyclophosphamide for 50 days (post-transplant days 18–67). Patients treated with plasmapheresis received an average of 10.4 ± 3.3 treatments (range 7–15), starting on post-transplant day 16.1 ± 9.9 (range 7–33 days) and ending on post-transplant day 32.6 ± 16.2 (range 17–59 days). Two of the seven treated patients and one of the six untreated patients lost their grafts to RNS ($p = \text{non-significant}$), yielding a total RNS graft loss rate of 23% (three of 13). Of the two plasmapheresis-treated patients who lost their grafts, each received only eight plasmapheresis treatments in total and both initiated plasmapheresis therapy within the first 2 weeks following Tx. None of the RNS patients who lost their grafts were treated with cyclophosphamide. Four of the nine NRNS patients lost their grafts because of chronic rejection within 5 yr following Tx.

The average time to follow-up was 62.3 ± 45.8 months (range 0.1–213.5 months). Patients with RNS who achieved remission had a significantly higher cumulative graft survival at 5 yr compared with RNS patients who did not achieve remission ($p < 0.001$, Fig. 1). Overall cumulative graft survival at 5 yr was not significantly different between the two groups (67% NRNS vs. 64% RNS, $p = \text{non-significant}$; Fig. 2). Donor source, induction therapy, primary non-function, or number of transplants did not significantly affect the overall 5-yr graft survival rate.

Discussion

We have shown that reversal of early RNS significantly improves long-term graft survival at a rate similar to that of patients with NRNS. The present findings are similar to those of Wuhl et al. who studied 39 pediatric patients and identified a 30% rate of recurrence, with a similar rate of graft survival between the RNS and NRNS groups (19).

Although the pathogenesis of RNS is probably the result of a circulating factor or group of factors, it is conceivable that idiopathic NS in children is not a single disease entity. The incidence of NS is higher in African-Americans than in other racial groups (20), and NS is more aggressive in African-Americans (21), but there is a lower risk of post-transplant recurrence (4). Moreover, a familial form of NS has been recently characterized, with the phenotype manifest as a structural abnormality in the glomerular basement membrane (22, 23); to date, there are no reports of post-transplant recurrence. However, it is the aggressive form of NS, with abrupt recurrence after Tx, which is a significant cause of end-stage renal disease in children and responsible for graft loss. This form of the disease is clearly the result of a circulating abnormality or factor with renal-specific effects.

RNS presents a unique clinical model for the study of native NS in that a relatively healthy kidney is placed in a poorly understood milieu containing elusive pathogenic changes. While

plasmapheresis is an effective therapy for many patients with RNS, it is not without significant risks and potential toxicities. Plasmapheresis is an invasive procedure, requiring central venous access, which can lead to thrombosis in the hypercoagulable state, characteristic of relapsed NS. In addition, the administration of blood products results in at least two major risks for the immunosuppressed patient. First, the transmission of viruses may result in a primary viral infection with significant morbidity and mortality. Second, unless the blood products are donor-specific, the risk of increased antigenicity and potential incitement of acute rejection poses yet another risk in the early post-transplant period. As it is, RNS is associated with a higher risk of acute rejection (24). Catheter-associated complications include bacteremia/septicemia, and thrombosis and/or stenosis of the great vessels.

Although there were no plasmapheresis-related adverse events in our small group, there remains a need for the development of therapies for RNS that are more specific and less invasive. Prospective multi-center studies in RNS are necessary for the development of therapies to prevent the progression of native NS to end-stage renal disease in children, as well as for the development of less toxic therapies to counter RNS.

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Fig. 1. Cumulative graft survival for recurrent nephrotic syndrome (RNS): remission vs. non-remission.

Fig. 2. Cumulative graft survival: recurrent nephrotic syndrome (RNS) vs. non-recurrent nephrotic syndrome (NRNS).