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Risk Factors for Chronic Graft Dysfunction in 918 Renal Transplants

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CHRONIC rejection or chronic allograft dysfunction (CD) persists as one of the most prevalent causes of long-term kidney graft loss.[1,2] As a consequence, the long-term survival and half-life of grafts remains poor, despite optimistic results from a recent publication.[1] Chronic allograft dysfunction is a process of gradual destruction of the kidney graft, dominated by progressive vascular obliteration and other structural changes resulting in fibrosis.[3] The evolution to CD is caused by two types of factors: nonimmunologic and immunologic.[3,4] The aim of this study was to investigate the incidence, causes, and effects of CD among a series of 918 renal transplants.

PATIENTS AND METHODS

We analyzed 1000 consecutive renal transplants performed in our Institution between July 1980 and February 2001:985 were from cadaver and 15 from living related donors. To define CD we only considered grafts with a minimum survival of 6 months, excluding those transplants lost before 6 months regardless of the specific reason—technical, acute rejection (AR), or death.[5] We defined CD as a progressive decline in renal function with a serum creatinine (SCr) >2.5 mg/dL. (Patients with a stable suboptimal renal function were not considered.) When the 82 grafts lost before reaching 6 months were excluded, 918 transplants had at least a year of follow-up.

We investigated the following parameters from the donor (age, cause of death, perfusion solution, cold ischemia time [CIT], and SCr before retrieval), from the recipient (age, weight, associated pathology, HLA mismatches, and immunosuppression), and from the transplant course (delayed graft function [DGF] and AR). We also studied AR and graft loss due to CD, and the influence of cyclosporine (CyA) dosage and SCr at 1 year on CD. We did not consider sensitization because the panel reactive antibody (PRA) level was irrelevant (2%). The cytomegalovirus status was not available.

A database was constructed from the records of all donors and recipients. A multivariate analysis was performed using logistic regression and univariate techniques and the Fishers Exact Test. We used the Kaplan Meier method to calculate survival and the log-rank test to compare survival rates between the two groups (with CD or without CD). For all tests, a P value $< .05$ was considered significant (two-tailed).

RESULTS

The CD was diagnosed in 239 (26%) of the 918 renal transplants. Multivariate analysis showed that the risk factors for CD were donor age >45 years (46% vs 22%), cerebrovascular stroke as cause of death in cadaver donors (40% vs 25%), graft perfusion with Euro-Collins solution (37% vs 19%), DGF (40% vs 25%), and AR (44% vs 16%) (Table 1). The immunosuppressive regimen of azathioprine (Aza) + prednisone (Pred) was associated with the highest (37%) incidence of CD and mycophenolate mofetil (MMF) + CyA + Pred with the lowest (13%) risk. In this series of renal transplants, CD emerged as the second cause of graft failure, with a rate of 30.6%, after death with a functioning graft (DWFG) with a 40.6% rate. We found a clear influence of AR on CD as a cause of graft loss: with 0, 1, or >1 AR episodes the graft loss due to CD was 22%, 43.5%, and 59%, respectively. The 1-year SCr significantly correlated with later development of CD (40% of CD with SCr >1.2 mg/dL vs 12% of CD with SCr <1.2 mg/dL). Graft survival rates at 1, 3, 5, 10, and 15 years were 98%, 86%, 68%, 36%, and 23% in the CD group, respectively, and 99%, 95%, 92%, 84%, and 74% in the group without CD, respectively. These differences in graft survival were statistically significant ($P = .000$) (Fig 1). Patient survival rates at 1, 3, 5, 10, and 15 years were 99%, 96%, 90%, 70%, and 57% in the CD group, respectively, and 99%, 96%, 92%, 85%, and 75% in the group without CD, respectively. These differences in graft survival were also statistically significant ($P = .0016$).

DISCUSSION

The exceptional graft and patient survival results, mainly in the first year, are a consequence of having excluded from the study all grafts that were lost before reaching 6 months' survival.

Like many other investigators, our results (Table 1) have shown the influence of donor age (>45 years) and AR in the development of CD.[2,3] Kidneys from pediatric donors (<15 years) and from older donors (>55 years) were associated with poorer results,[6] probably related to their reduced nephron mass, favoring a hyperfiltration process (mainly when creatinine clearance is less than 60 mL/min) with functional overload and subsequent tissue damage of the remaining renal mass.[3,4,6] Acute rejection, with its

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Table 1. Risk Factors for Chronic Allograft Dysfunction

Factors	*P* Value	Odds Ratio	CI 95%
Donor age >45 years	.000	3.563	2.303–5.508
Donor cause of death (CVS)	.033	1.706	1.044–2.788
Perfusion with Euro-Collins solution	.000	3.207	2.304–4.464
CIT	NS		
Recipient age	NS		
Recipient weight	NS		
Recipient-associated pathology	NS		
HLA mismatches	NS		
Azathioprine + prednisone	.000	2.675	1.422–5.636
DGF	.027	1.573	1.068–2.317
Acute rejection	.000	4.074	2.976–5.579
CYA dose >5 mg/kg/d at 1 year	NS		
SCr at 1 year >1.2 mg/dL	.000	4.871	3.475–6.864

Abbreviations: CVS, cerebrovascular stroke; CIT, cold ischemia time; DGF, delayed graft function; CYA, cyclosporine; SCr, serum creatinine.

immunological injury, is the factor most relevant to the high incidence of CD.[2,3,7] The AR episodes are associated with local cytokine release, inducing progressive nephron damage and renal mass destruction, with development of a fibrotic repair that ends in CD.[3] Hyperfiltration of the remnant nephrons, leading to glomerulosclerosis, also plays a role in the evolution to organ failure.[3,7]

Our analysis also demonstrated a powerful influence of AR in the development of CD (Table 1): in the absence of AR the CD rate was 16%, but with one or more AR episodes CD appeared in 44% of cases. We correlated AR with CD and with graft loss, concluding that both CD and graft losses were strongly influenced by previous AR: without AR, 22% of the graft losses were due to CD and with one AR episode, 43.5% of the graft losses were caused CD.

Another factor that appeared to have influence on the development of CD was the perfusion solution. (Table 1). Grafts perfused with University of Wisconsin (UW) solution showed better outcomes. Immunosuppression also had a significant influence on the occurrence of CD. The immunosuppressive regimen with MMF was associated with a lower rate of CD. We must be cautious as the follow-up of our patients treated with MMF is relatively short (4 years), but the significant decrease in AR incidence with MMF allows us to hope, in the future, for a corresponding reduction in CD.[8] One of the most interesting findings in our study was the significant predisposition for patients with SCr >1.2 mg/dL at 1 year to develop CD, particularly considering that we excluded grafts that were lost in the first 6 months. In these patients we observed a higher risk (Table 1) for CD, probably because many patients had began the evolution to CD in the first year after transplantation, as is suggested by others.[5]

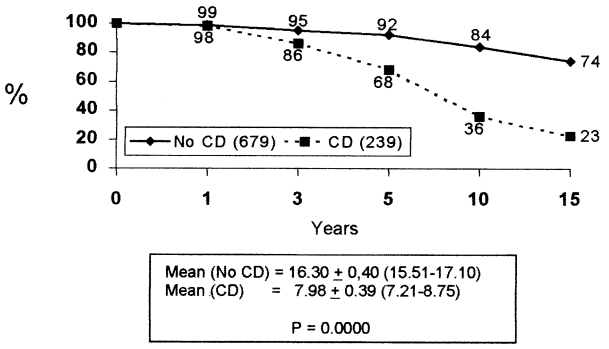

Fig 1. Comparison of graft actuarial survival without CD and with CD (Kaplan-Meier Method.

To prevent CD it is essential to decrease graft injury by both immune and nonimmune mechanisms,[7] a goal that may be achieved by reducing the number and severity of AR episodes with more effective and less toxic immunosuppression and by optimizing the age and weight matching between donor and recipient.[9] This strategy and the new immunosuppressive agents may explain why Takemoto et al[5] observed a tendency to a reduction in the incidence of CD from 1995 to 1998, accompanying a decreased AR rate.

In this study we conclude that older donor age, perfusion with Euro-Collins solution, immunosuppression with azathioprine and prednisone and mainly acute rejection episodes were most significant risk factors for CD. In our series CD emerged as the second cause of graft loss, namely 30.5%. The CD contributed significantly to poorer graft survival and patient survival. An SCr level above 1.2 mg/dL at the end of the first year prematurely anticipates the later development of CD.

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