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ORIGINAL ARTICLE

Decreased short-term renal graft survival in Maghrebian recipients

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Abstract The influence of race on renal allograft survival is disputed. We studied 16 cadaveric renal transplants in 14 Maghrebian patients, each matched with two controls of local origin. Patient survival at 12 months was 93% in the Maghreb group and 97% in the control group (NS). Graft survivals at 3 months for these two groups were 73% and 97%, respectively ($P < 0.01$). At 6 months, graft survival in the control group remained unchanged at 97%, whereas in the case group it declined further to 59% ($P < 0.01$). Overall graft failure in the Maghreb group amounted to 44% (seven of 16 transplants). In each case, failure was due to biopsy-proven acute rejection. Overall graft failure amongst the controls was only 6% (two of 32 transplants) ($P = 0.004$) (only one case of acute rejection, or 3%) ($P = 0.01$). This study provides evidence for significantly lower short-term renal graft survival in Maghrebian recipients of a Caucasian graft. Acute rejection seems to play a major causative role in graft loss in this group.

Keywords Kidney transplantation · Maghreb · High-risk population · Acute rejection

Introduction

Since Opelz et al. [15] first reported significantly worse 1-year renal graft survival in African Americans than in Caucasians, the influence of race on the success of renal transplantation has remained controversial. Reflecting the changing make-up of society in western Europe, an increasing number of non-Europeans living in Europe have undergone renal transplantation [17]. This is borne out in our center by a number of cadaveric renal transplantations in patients originating from, amongst others, the Arab countries of Morocco, Algeria, and Tunisia, the so-called Maghreb countries located in the northern part of the African continent. Useful information about cadaveric renal transplantation from Arab countries is sparse, as the overwhelming majority of kidney transplantations performed are from living related donors [1, 3]. Graft and patient survival were studied in the first year after transplantation, as was overall graft survival in the Maghreb recipients of Caucasian grafts as compared to matched controls of local origin. Furthermore, a number of other relevant characteristics, including reason for transplant loss as reported in the Eurotransplant register, were collected and compared.

Materials and methods

A total of 16 transplants in 14 Maghrebian recipients were compared with 32 controls of local origin, matched for gender, age, and period of transplantation, from the total transplantation population of the Antwerp center, comprising 369 patients. All 369 patients were transplanted in the University Hospital Antwerp after 1985 and before 2000. To exclude transplantations from the precyclosporine era, none earlier were studied. To minimise the effect of possible confounding factors, matching took place according to gender, age (within 5 years higher or lower), and period of transplantation (1985–1989, 1990–1994, 1995–1999), the latter to limit effects of changes in immunosuppression strategies, in

particular due to the introduction of new drugs. In the period from 1985 to 1989, a total of 98 patients were transplanted, of whom three were of Maghrebian origin. In the following period (1990–1994), 146 patients were transplanted (six Maghrebians), and in the period from 1995 to 1999, 125 were transplanted (seven Maghrebians). Combined organ transplantations (for example kidney-pancreas) were excluded, whereas second transplantations were admitted and studied in both groups.

Information pertaining to age, gender, cause of loss of native renal function, cold ischemia time, donor age, number of mismatches on the human leukocyte antigen (HLA) A, B and DR loci, time on the transplantation waiting list, and the number of previous transplants were gathered using the Eurotransplant register. Furthermore, where applicable, time from transplantation to transplant loss and reason for loss were noted. In case of graft loss, all pertinent biopsies were reviewed to verify the accuracy of the reason for graft loss recorded in the register. At the time of analysis, all patients had at least 1 year of follow-up.

Statistical analyses were performed using SPSS software (version 10.0 for Windows, SPSS, Chicago, Ill., USA). Independent sample *t*-test, chi-squared test, and Fisher's exact test were used, as appropriate, to compare the demographic characteristics, acute rejection, overall graft failure, and patient survival at 12 months between the two groups, with the significance level set at $P = 0.05$. Graft survival in the two groups was displayed by Kaplan-Meier survival curves. Differences in graft survival were estimated by the log-rank test.

Results

As shown in Table 1, 16 Maghreb transplant recipients (11 male, 5 female) were matched with 32 controls of local origin for age, gender, and period of transplantation. Two transplants in the Maghreb group were second transplants, compared to four in the control group. There were no statistically significant differences between the two groups for recipient age, cold ischemia time, donor age, or time on the waiting list for transplantation.

Although there were no statistically significant differences in HLA matching in total, there was a trend towards worse HLA matching in the Maghrebian group. However, if one studies matching on the HLA-DR locus separately, this is significantly worse in the Maghrebian group. For each HLA locus, the number of zero mismatch transplantations was higher in the control group. No patient in the Maghrebian group had zero mismatches on all three loci, compared to three in the control group.

In Table 2, the causes of native renal function loss, as registered, are given both for the Maghreb and control groups. Although in more than a third of cases no exact cause was determined, it is important to note that cases of nephroangiosclerosis as a cause of renal function loss in the Maghreb group far outweigh those in the control group (five cases, or 31%, vs one, or 3%). Diabetes as cause of loss was only found in the control group (total of three cases, or 9%), and polycystic kidney disease, too, was far more common amongst the controls (six cases, or 19%, vs one case, or 6%).

When comparing acute rejection leading to graft loss in our transplant population of 369 patients in the three periods studied, a decline in incidence is found. In the period from 1985 to 1989, 11 patients out of 98 (11.2%) lost their renal graft due to acute rejection. In the period from 1990 to 1994, this number was eight out of 146 (5.5%). From 1995 to 1999, six out of 125 patients (4.8%) lost their grafts for this reason. If in these three periods we exclude the transplants in Maghrebian

Table 2. Causes of native renal function loss in Maghreb and control groups

Cause of native renal function loss	Maghreb ($n = 16$)	Controls ($n = 32$)
Glomerulonephritis, cause unknown	5 (31%)	10 (31%)
Kidney insufficiency, cause unknown	1 (6%)	2 (6%)
Polycystic kidney disease	1 (6%)	6 (19%)
Pyelonephritis/interstitial nephritis	1 (6%)	1 (3%)
Reflux nephropathy	0	1 (3%)
Dense deposit disease	1 (6%)	0
Goodpasture's disease	0	1 (3%)
IgA nephropathy	0	2 (6%)
Nephroangiosclerosis	5 (31%)	1 (3%)
Renovascular	0	1 (3%)
Diabetes mellitus type I	0	2 (6%)
Type II	0	1 (3%)
Hereditary/familial type, unspecified	0	1 (3%)
Alport	0	1 (3%)
Lupus nephritis	1 (6%)	0
Congenital renal dysplasia	1 (6%)	1 (3%)
Secondary focal sclerosis and hyalinosis	0	1 (3%)

Table 1. Demographics of Maghrebian and control (local origin) transplant recipients

	Maghreb ($n = 16$)	Controls ($n = 32$)	*P* value
Mean age in years (SD)	38.2 (12.7)	39.6 (11.9)	0.715
Gender (M/F)	11/5	22/10	–
Mean cold ischemia time in hours (SD)	23.1 (6.8)	22.4 (7.9)	0.773
Mean donor age in years (SD)	40.4 (16.9)	34.9 (17.2)	0.314
Mean waiting time in months (SD)	16.3 (14.9)	21.9 (25.7)	0.486
Mean mismatches in A and B (SD)	2.19 (0.66)	1.94 (1.08)	0.325
Mean mismatches in DR (SD)	0.81 (0.40)	0.50 (0.51)	0.026
Mean mismatches in total (SD)	3.00 (0.82)	2.44 (1.22)	0.065
Percent of zero HLA mismatches in total	0	9.4	0.529
No. of second transplants	2	4	–

patients altogether, the percentages are 10.5%, 3.5%, and 2.5%, respectively. It can therefore be concluded that in the final 5-year period studied, acute rejection in Maghrebian patients accounts for half the total number of acute rejections.

The results for graft survival in Table 3 show statistically significant differences in graft survival, particularly in the first 6 months after transplantation (see also Fig. 1) favouring the control group. Despite the fact that from then onwards graft survival was similar in both groups, overall graft survival was worse in the Maghreb group ($P=0.004$). Patient survival at 12 months was 93% in the Maghreb group, as compared to 97% in the control group (NS). None of the transplant recipients in either group died with a functioning graft. All grafts lost (seven of 16) in the Maghreb group were due to biopsy-proven acute rejection. Only one of the 32 grafts lost in the control group was caused by acute rejection ($P=0.01$).

In Fig. 1 a Kaplan-Meier survival curve illustrates the differences in graft survival between the two groups.

Discussion

The issue of the effects of race on renal transplant survival remains contentious, despite overall renal graft survival improving over recent years. Although much has been published on this subject, opinions remain divided concerning the causes of differences in renal graft survival. The overwhelming majority of studies have taken place in the United States of America, studying graft survival in African American transplant populations in comparison to Caucasians.

To our knowledge, there has been only one study [17] in which graft survival in a similar population to ours and transplanted in similar circumstances has been described. Roodnat et al. [17], while comparing renal graft survival after primary cadaveric transplantation in native and non-native European recipients, studied a total of 11 recipients of Arab descent, two from the Middle East and nine from Morocco. This group had a significant relative risk of 3.6 for graft failure, the highest of all groups studied, higher even than those of black African descent, who had a relative risk of 2.0. No detailed information was given about the causes of graft failure nor was the length of time from transplantation to graft failure discussed.

Roodnat et al. [17] claimed that, because the organisation of the medical health system in the Netherlands assures equal access for all inhabitants, socio-economic circumstances could not explain the differences between the racial groups in their study. As access to health care in Belgium is similar to that in the Netherlands and considering that we found differences in graft survival in a period when the patient was either still in hospital or in intensive outpatient follow-up (2 to 3 times a week), neither lack of therapeutic compliance nor socio-economic circumstances seem to be likely explanations for our findings.

Useful information from Arab countries concerning renal graft survival is sparse and its value limited, since most information concerns living related donor transplantations, often including transplantations from the pre-cyclosporine era [1, 3]. Furthermore, it should be noted that the large majority of transplantations (LRD) in Arab countries are within the same race, whereas the overwhelming majority of kidney donors within Eurotransplant are Caucasian, thereby rendering the

Table 3. Graft and patient survival in the Maghreb and control groups

	Maghreb	Controls	*P* value
Patient survival at 12 months	93%	97%	0.419
Graft survival at 3 months	73%	97%	< 0.001
Graft survival at 6 months	59%	97%	< 0.001
Graft survival at 12 months	59%	97%	< 0.001
Overall graft survival	44%	93%	0.004

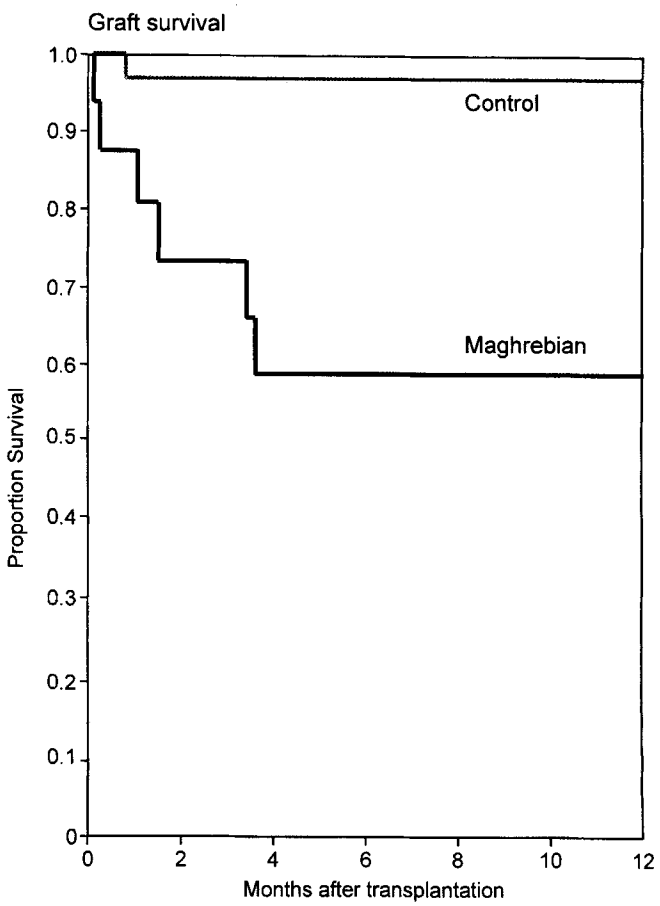

Fig. 1. Kaplan-Meier curves for graft survival in first year after transplantation in Maghreb and control groups

transplantations we studied interracial, as in reference [17]. We conclude that the findings of our study, together with those described by Roodnat et al., identify a new high-risk population for decreased kidney allograft survival.

Studies have demonstrated the risk of poorer HLA matching to be higher with donor and recipients of different race [2, 10]. In the present study, in transplants with differing donor and recipient race, we demonstrated significantly worse HLA matching on the DR locus in the Maghrebian group. However, Koyama et al. [9] provided evidence questioning the primary role of HLA matching on graft survival: African American recipients demonstrated more graft rejection after renal transplantation from HLA identical donors than Caucasians. Neither the influence of differences in donor race nor HLA differences at DNA level nor socioeconomic factors could be excluded. There is evidence pointing to a lower beneficial influence of HLA matching on short- and long-term living related kidney survival in African Americans than in the non-African American population [7, 14], thereby excluding the effect of racial difference between donor and recipient. Again, it must be stressed that these studies describe a different high-risk population from ours, and therefore extreme caution is warranted when extrapolating these findings to the Maghreb transplant recipient population.

The role of acute rejection and its effect on long-term renal allograft survival have come increasingly under scrutiny. Inferior outcome in 2-haplotype (living related donor) matched renal transplants in African Americans compared to Caucasians has been described [14], whilst a significantly higher incidence of acute rejection and delayed graft function was found in the African American group in the same study. These findings of higher incidence of both acute rejection [12] and delayed graft function [5] have been corroborated elsewhere.

Not only have racial differences in immune response been proposed as underlying mechanism for differing outcomes [6, 8], but also a unique haplotype has been put forward, identifying an African population at increased risk for transplantation rejection [4]. A potential role for minor histocompatibility complex antigen differences can not be ruled out. There is evidence for a genetic predisposition towards acute rejection after renal transplantation, based on differences in genetically encoded cytokine production capacity [16]. Although Pelletier et al. [16] could not reveal significant racial differences in cytokine phenotype frequencies, statistical significance could well be reached in a much larger patient cohort. Although these possible explanations offer no clinical benefit at present, the finding that, while African Americans are at increased risk for acute rejection, they demonstrate a decreased risk for death due to infection under immunosuppression [12] may have implications for immunosuppressive strategies [11, 13].

In summary, a significantly lower short-term renal graft survival in Maghrebian recipients was demonstrated in our study. Acute rejection seemed to play a major causative role in graft loss in this group. Since these differences were found in a period when the patients were either still in hospital or in intensive outpatient follow-up, lack of therapeutic compliance seems to be an unlikely explanation. It is important to stress that the results of this study are based on a small group of patients and must be confirmed by larger studies. Although extreme caution should be exercised to avoid misinterpretation of results, risking negative discrimination of subpopulations, registration of race in the Eurotransplant register as practised in the United Network for Organ Sharing (UNOS) transplant register would, we feel, provide valuable information about variations in transplant outcome in different subpopulations and effects of differing immunosuppressive strategies.

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