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Immunological risk factors are solely responsible for primary non-function of renal allografts

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Abstract Primary non-function (PNF) of renal allografts has been attributed to various risk factors, among them immunological ones, as well as unfavourable preservation conditions. To investigate the impact of these risk factory on the occurrence of PNF, 1335 consecutive kidney transplants performed at a single centre over a 10-year period were analysed. All patients received immunosuppression based on cyclosporine. As the method of analysis a conditional stepwise logistic regression model was chosen, comparing each graft suffering PNF with its partner kidney retrieved from the same donor. Thus, all donor-related variables could be omitted from the analysis, as they are the same in every pair of grafts. Risk factors analysed included panel-reactive antibodies, number of pretransplant transfusions, pregnancies, number of prior transplants, cold and second warm ischaemia time, mismatches on HLA loci A, B and DR and recipient age. The overall incidence of PNF was 87 grafts (6.5%). One patient suffered immediate rejection due to transplantation of an ABO incompatible graft. This case was excluded from further analysis. PNF occurred three times in recipients of living related grafts, twice in recipients of en-bloc grafts and four times in grafts, in which the paired kidney was either not transplanted or shipped outside the Eurotransplant region, so that no paired graft was available for matched case-control analysis. Of the remaining 77 pairs, twice both organs of one donor failed immediately. The remaining 73 complete pairs were analysed. Two of the investigated risk factors have independently a significant impact on the occurrence of PNF. Increasing the number of pretransplant transfusions raises the relative risk of graft failure up to six fold ($P=0.02$), while a history of prior transplants bears a relative risk of 0.21E05 ($P=0.005$). Ischaemia has no significant impact on the occurrence of PNF. Our data strongly suggest that immunological rather than donor risk factors are responsible for the non-function of kidney grafts.

Key words Renal transplantation
Primary non-function
Immunological risk factors

Introduction

The total lack of functioning of a graft (primary non-function, PNF) is a phenomenon contributing to the incidence of graft loss in all kidney transplant centres at rates of up to 15% [1]. The occurrence of PNF has been attributed to several factors, both on the donor and on the recipient side, including donor age, donor procurement factors like circulatory conditions or duration of hospital stay, factors concerning organ procurement and ischaemic time, and donor factors like rejection [2–4]. PNF has mostly been dealt with among other forms of initially impaired graft function such as initial non-function or early graft failure [2–4], while our intention was to focus only on grafts which never functioned.

The present analysis was based on the availability of both kidneys of each donor, which were transplanted into different recipients. Donor and procurement factory should be expected to be the same in such paired kidneys, which offers the possibility of omitting donor factors from further analysis in order, to concentrate on differences in cold ischaemic time and recipient risk factors.

Patients and methods

A 10-year series (1982–1991) of 1335 consecutive renal transplant patients, grafted at the Vienna transplant centre and followed up prospectively, formed the basis for our analysis. All patients received an initial immunosuppression regimen based on cyclosporine as described in detail elsewhere [5].

PNF was defined as a continuous need for dialysis following transplantation, without ever achieving sufficient graft function. For all grafts suffering PNF, information about the fate of the paired kidney including detailed recipient data was obtained. Whenever PNF occurred in kidneys shipped to our centre via Eurotransplant (ET), data about the partner graft and its recipient were obtained at the specific transplant centre. In the same way, data concerning paired grafts given from local donors to other ET centres were collected. Risk factors obtained and analysed for each pair of organs/recipients were: shipped or locally transplanted kidney (OR), cold ischaemic time (CIT), second warm ischaemic time (WIT), recipient's age (RA), history of prior transplants (PT), latest panel-reactive antibodies (PRA), number of pretransplant transfusions (BT), pregnancies (PR), mismatches of HLA loci A, B and DR (MMA, MMB, MMDR) and graft performance. These risk factors were graded as shown in detail in Table 1.

Statistical analysis

A matched case-control study using a stepwise conditional logistic regression was carried out to detect differences in risk factors between recipients of paired grafts. Univariate analysis (chi-square tests) was carried out as a first step for all relevant risk factors potentially affecting graft survival (Table 1). All factors with a statistically significant impact or a trend towards a significant impact on the occurrence of PNF were entered into the regression model. For grafts with missing information on paired kidneys, donor factors were also analysed. For all partner kidneys of PNF grafts that showed initial function, Kaplan-Meier survival estimates were calculated and compared with the overall graft survival of primarily functioning renal transplants at our centre.

Table 1 Distribution of risk factors in primary non-function (PNF) patients and controls (abbreviations are defined in the text, *RR* relative risk)

	PNF	Controls	χ^2	RR
	n (%)	*n* (%)		
PRA				
0%	41 (56)	49 (67)		
1–40%	11 (15)	16 (22)	0.04	NS
>40%	21 (29)	8 (11)		
BT				
0	3 (4)	11 (15)		
1–5	17 (23)	35 (48)	0.01	1.7
>5	55 (73)	27 (37)		5.8
PR				
0	49 (67)	62 (85)		
1–2	17 (23)	6 (8)	0.03	NS
>2	7 (10)	5 (7)		
PT				
0	52 (71)	66 (90)		
1	10 (14)	7 (10)	0.002	1.4
>1	11 (15)	0 (0)		0.21E05
MMA				
0	27 (37)	25 (34)		
1	37 (51)	43 (59)	NS	NS
2	9 (12)	5 (7)		
MMB				
0	12 (16)	10 (14)		
1	47 (64)	55 (75)	NS	NS
2	14 (19)	8 (11)		
MMDR				
0	39 (53)	37 (51)		
1	33 (45)	34 (47)	NS	NS
2	1 (1)	2 (3)		
OR				
local	50 (68)	47 (64)		
shipped	23 (23)	26 (36)	NS	NS
	median (95% CI)	median (95% CI)		
CIT (h)	23 (14–35)	24 (12–38)		NS
WIT (min)	38 (20–77)	42 (22–80)		
RA (years)	41 (22–66)	46 (18–63)		NS

Results

PNF was observed in 87 cases (6.5%) in 85 patients. In one patient immediate graft loss occurred due to the

Table 2 Graft survival rates for functioning paired grafts (PG) and all primarily functioning grafts (PFG) of the patient series 1982–1991

Rates at:	1 year	3 years	5 years
PFG	88.7±1	79.2±1	71.0±1
PG	86.5±4	79.5±5	75.1±5

unitentional transplantation of an ABO incompatible kidney. This case was excluded from further analysis. Three recipients of living related grafts suffered PNF, two en-bloc grafts never showed function, and in four cases either only one kidney of a donor was retrieved or the second graft was transplanted outside the ET region and no follow-up was available. Thus, 77 cases of PNF remained for further matched case-control analysis. Twice, both organs of one donor failed immediately. In all remaining 73 pairs one graft each suffered PNF while the respective partner kidney functioned, showing cumulative graft survival rates of 86±4% at 1, 79±5% at 3 and 75±5% at 5 years after a median follow-up of 31 months (Table 2).

Univariate analysis showed a significant impact on graft survival for PRA, PR, BT and PT. These factors were further investigated in a multivariate analysis.

Stepwise conditional logistic regression procedures revealed a significant independent impact for BT and PT. While 5–10 preoperative transfusions increased the likelihood of PNF by 1.7 ($P = 0.02$), transfusion of more than 10 BT caused a sixfold increase of the risk of immediate graft loss ($P = 0.02$). PT of one prior transplant shows a moderate increase of the risk of PNF by 1.4 ($P = 0.005$). In contrast, PT of two or more prior transplants results in an extreme increase in the relative risk of 0.21E05 ($P = 0.005$).

Analysis of donor risk factors for the pairs showing PNF in both grafts or for PNF grafts without an available control kidney did not reveal significant differences in comparison with the cohort of donors of functioning grafts. Both recipients of en-bloc grafts had elevated PRA; additionally, one of them had a history of a prior transplant. In two of the living related donor/recipient pairs, the donors exhibited no evidence of risk factors for PNF, while in one pair, the donor was 70 years old and the recipient had 40% PRA. MLC was negative in all cases.

Discussion

The occurrence of PNF is a well-known complication of renal transplantation, but the phenomenon itself has hardly ever been investigated [4]. In most publications PNF is dealt with among other forms of early graft failure or initial non-function [1, 3, 4], which makes comparison of the published data difficult. Moreover, only a few investigators chose the case-control approach using the paired kidney as the control [6].

Several factors both on the donor and on the recipient side were held responsible for the primary failure of renal grafts [2–4]. Donor age, donor hypotension, duration of ICU stay or prolonged ischaemia were risk factors causing graft damage before transplantation [2, 4]. On the recipient side mainly immunological factors were addressed, including all forms of recipient sensitisation such as duration of dialysis, pretransplant polytransfusion, prior transplants or the existence of panel-reactive antibodies [2–4]. Since the introduction of CsA and the detection of its nephrotoxic potency [7], excessive initial CsA levels have also been suspected of being responsible for early graft loss. There are, however, reports in which no differences were found in the pattern of factors causing initial or primary graft failures when comparing the eras of conventional (steroid and azathioprine) and CsA-based immunosuppression [1, 2].

Our study setting enabled us to omit the donor data completely from the analysis and thus concentrate on fewer variables. For the grafts lacking controls, no definitive statement concerning the role of donor risk factors can be made, although none of these donors showed any deviations concerning age, circulatory condition or cold ischaemia duration from the average of our donor population.

Although the operation protocols of the two cases of en-bloc grafts in our series report no technical difficulties, this type of transplant retrieved from paediatric donors seems to bear a high risk of technical complications and may certainly not be directly compared with the remaining cases of PNF. Moreover, grafts from very young donors have repeatedly been reported to fare badly in adult recipients [8].

Concerning the recipients of related renal grafts, different causes for the occurrence of PNF have to be discussed. While in two of these cases donors as well as recipients evidenced no risk factors for such an immediate graft failure, in one related couple donor and recipient risk factors were present. PNF in both grafts harvested from one donor occurred in two cases. Although in both cases no clearly unfavourable donor condition was detectable in the donor files, it is most likely that suboptimal graft conditions, perhaps in connection with recipients at a higher risk for graft failure, were responsible for PNF.

In all remaining pairs, the partner kidney of a PNF transplant showed sufficient function. Overall graft survival in these recipients for up to 5 years did not differ from the corresponding graft survival rates in the cohort of all primarily functioning graft at our centre during the study's observed period. The fact that in 95% of the here reported cases an immediately failing graft has a normally functioning parameter organ strongly suggests a major influence of recipient factors on the occurrence of PNF.

Case-control analysis of the paired kidneys revealed a large impact of predisposing immunological properties of the recipient, like pretransplant polytransfusion and especially multiple prior transplantation. In the present series increasing levels of PRA did not have an independent detrimental effect on the transplantation outcome. Most patients with a history of multiple transplantation bore a high risk of elevated PRA [9], so that the negative effect of high PRA levels may be masked by the simultaneous presence of the very strong risk factor "multiple transplantation". The factor "ischaemia", at least in our series, has no relevance whatsoever in explaining the occurrence of PNF. The CIT even tended to be longer in functioning grafts.

As all these recipient properties increasing the risk of PNF are present at the time of transplantation, the aim of a therapeutic programme will have to be to minimize their detrimental effect not only by adequate immunosuppression [6], but also by an effective mode of depletion of present or subclinically effective antibodies. Early experiences with a method of recipient immunoapheresis may indicate a successful solution for this problem.

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