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The effect of acute rejection on long-term renal graft survival is mainly related to initial renal damage

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Abstract It has been suggested that poor long-term prognosis of acute rejection is due to hyperfiltration-mediated injury secondary to the initial renal damage, rather than to ongoing immunological mechanisms. A total of 953 renal transplant recipients was reviewed to examine the effect of acute rejection episodes on graft function and survival; 40 % had no rejections, 45 % one, 12 % two and 3 % three. Rejection episodes adversely affected short- and long-term prognosis (5-year survival for no rejections, 62 %; one, 34 %; two, 26 %; three, 19 %, $P < 0.001$) and creatinine clearance at one year (cl 1) (none, 56.7 ml/min; one, 51.1; two, 52.9; three, 35.2, $P < 0.01$). This was mainly due to increased graft loss, but patient survival was also reduced (5-year survival for no rejections, 77 %; one, 76 %; two, 63 %; three, 53 %, $P < 0.05$). There was no overall effect of rejection number, independently of cl 1. However, subgroup analysis showed a detrimental effect of rejection number on grafts with high residual function, i.e. cl 1 > 60 ml/min (5-year graft survival none and one, 87 %; two and three, 71 %, $P < 0.01$). Late initial rejection episodes adversely affected prognosis (5-year survival 1–7 days, 34 %; 8–60, 31 %; 60–300, 21 %, $P < 0.05$) and residual graft function (cl 1 1–7 days, 56.2 ml/min; 8–60, 48.7; 60–300, 44.6, $P < 0.01$). In conclusion, the poor long-term prognostic effect of rejection episodes is mainly, but not entirely, related to initial graft destruction. Late (> 2 months after transplantation) initial rejection is an important independent risk factor for graft loss.

Key words Renal transplantation · Chronic rejection · Hyperfiltration

Introduction

Acute rejection is the major cause of graft loss during the first year following renal transplantation. Acute rejection episodes, even after successful treatment, are also an important factor in predicting late graft loss [1–9]. Traditionally, this has been considered to be due to HLA mismatching causing, firstly, acute graft loss due to acute rejection and, secondly, chronic rejection, a long-term destruction of graft function due to repeated immunological injury [10–13]. In support of this, HLA mismatching is a powerful predictor of chronic graft loss [14]; in particular, HLA-identical siblings have an excellent long-term prognosis. Non-immunological causes for graft loss, in particular the hyperfiltration theory, have recently been proposed. The hyperfiltration theory suggests that loss of graft function is related to poor initial function relative to the recipient's size, causing hyperfiltration, increased glomerular blood flow and pressure, increased glomerular permeability characteristics, hypertrophy and progressive renal damage [11, 15–17]. It is therefore reasonable to ask whether the long-term deleterious effect of acute rejection episodes is secondary to initial renal damage, leading

to haemodynamically mediated injury, i.e. the relationship is essentially non-immunological in nature. The present study was performed to study the long-term effects of acute rejection episodes and their relationship to primary renal damage.

Materials and methods

Patients

Between the years 1968 and 1989, 800 patients received a total of 1020 renal transplantations at this center. Of these, 67 had no primary function; the remaining 953 were included in the study. The main cause of graft loss before 1 year was acute rejection. Acute rejection is rare after 1 year, the main cause of graft loss thereafter being chronic rejection. Therefore, for most analyses, only 590 transplants with graft survival > 1 year were included. Of these, 56% were male, the mean age was 40.3 ± 12.5 years, 8% received transplants from living donors, 88% were first transplants, 3% of the recipients were less than 16 years old and 42% were treated with cyclosporine. The primary renal diagnoses were: chronic glomerulonephritis, 38%; chronic interstitial nephropathy, 23%; nephrosclerosis and renovascular disease, 4%; polycystic renal disease, 10%; diabetes 4%; other (including end-stage renal disease of unknown origin), 21%.

Most of the organs during this period were harvested using heart death criteria. The immunosuppressive regime underwent several changes. Virtually all patients received high-dose steroids, tapered over several months to 5–10 mg prednisone daily. The treatment was combined with azathioprine (1–2 mg/day) between 1968 and 1983. Prednisone and cyclosporine were used between 1983 and 1986, when triple therapy was introduced. Since 1988, quadruple therapy has been used, involving 5–14 days of treatment with anti-lymphocyte globulin before the start of cyclosporine treatment. The non-specific cyclosporine concentration (Abbott) was maintained between 200 and 400 ng/ml (corresponding to a specific concentration of ca 50–150 ng/ml). The overall 1-, 5- and 10-year graft survival rates were 57%, 38% and 26% and the overall patient survival rates 90%, 78% and 59%, respectively. During the period of observation, 1-year graft survival improved from 50% to 83%. Acute rejection was always verified by biopsy and treated with high-dose steroids. The incidence of non-compliance, as judged by psychiatric disease, low or variable cyclosporine concentrations, poor outpatient attendance and acute graft rejection occurring after 1 year, was rare.

Methods

The following clinical data were recorded: donor source (living related/cadaver), donor age and sex, recipient age and sex, HLA compatibility (A, B, DR after 1980), warm ischaemia time, cold ischaemia time, posttransplant time to creatinine clearance > 5 ml/min, number of acute rejections, date of each rejection, graft survival time and patient survival time. Creatinine clearance was measured from a 24-h urine specimen 1 year after transplantation. Immunosuppressive therapy and blood pressure were recorded 3 and 12 months after transplantation.

Patient and graft survival were stratified according to the number of rejection episodes during the first year, the timing of rejection episodes, and residual renal function. Since the primary aim of the study was defining the aetiology of chronic graft loss, results were censored for patient death in most analyses.

Statistical analysis

Kaplan-Meier product-limit estimation was performed to compare survival. Categorical analysis was performed using ANOVA and Student's *t*-test.

Results

Only 23 acute rejections were diagnosed later than 1 year after transplantation, comprising 3% of the total number of rejections. These occurred sporadically 4.5 ± 3.0 years after transplantation and had a poor prognosis with a half-life of 1.5 years and a 5-year graft survival of 22% aftger diagnosis. These rejection episodes were excluded from further analysis.

Altogether, 40% of patients experienced no rejection episodes during the first year, 45% one, 12% two and 3% three episodes. There was no significant relationship between rejection number and transplant number, AB match, donor age and sex, or recipient age and sex. Patients experiencing rejections had a poorer DR match, were less often treated with cyclosporine, received higher doses of prednisone and azathioprine and less frequently had a living donor (Table 1). There was a tendency for these patients to have longer warm ischaemia times, shorter cold ischaemia times and more rapid graft function start. Their blood pressure was considerably high at 3 months and was still significantly high at 12 months.

The number of rejection episodes was a highly significant predictor of graft survival, both in the short and long term (Fig. 1). This difference was mainly due to increased graft loss, but patients experiencing more than one rejection episode also had an increased mortality (5-year patient survival: no rejection, 77%; one, 76%; two, 63%; three, 53%, $P < 0.05$). The causes of death are shown in Table 2. The main cause of excess mortality was a 34% increase in the proportion of atherosclerotic and cardiac death, there being no increased proportion due to infection or cancer. Subgroup analysis (0–2 years and > 2 years posttransplant) yielded similar results. Rejection episodes significantly reduced creatinine clearance at 1 year: none, 56.7 ± 21.2 ml/min; one, 51.1 ± 21.2; two, 52.9 ± 18.9; three, 35.2 ± 24.9, $P < 0.01$.

Patients with graft survival longer than 1 year were censored for patient death and stratified into four groups according to creatinine clearance at 1 year: 6–20, 20–40, 40–60 and > 60 ml/min. Graft survival was substantially different in the four groups, the half-life being 2.5, 9, 21 and 27 years, respectively ($P < 0.001$). There was no significant influence of rejection number on graft survival in the first three groups (Fig. 2 A), while patients with a creatinine clearance > 60 ml/min at 1 year had a worse prognosis if they had suffered

Table 1 Relationship between rejection number and clinical variables (*NS* not significant)

Clinical variable	Rejection number				*P* value
	0	1	2	3	
DR match	1.15 ± 0.62	0.89 ± 0.61	1.04 ± 0.52	–	< 0.01
Living, related donors (%)	7.1	3.5	1.8	3.8	< 0.05
Cyclosporine treatment (%)	40	27	10	4	< 0.001
Prednisone dose at 12 months (mg/day)	12.0 ± 4.5	14.5 ± 4.9	18.6 ± 8.8	16.2 ± 4.2	< 0.001
Azathioprine dose at 12 months (mg/day)	72.7 ± 51.7	89.1 ± 41.3	100.0 ± 30.1	90.9 ± 37.5	< 0.001
Time to creatinine clearance > 5 ml/min (days)	6.9 ± 7.7	5.3 ± 6.9	5.7 ± 7.9	5.4 ± 7.4	< 0.05
Warm ischaemia time (min)	13.5 ± 12.0	12.4 ± 11.3	15.4 ± 14.5	16.5 ± 16.5	0.07
Cold ischaemia (h)	16.9 ± 8.6	17.2 ± 7.9	15.7 ± 7.5	13.3 ± 9.1	0.06
Systolic pressure					
3 months (mm Hg)	145 ± 23	150 ± 23	157 ± 23	161 ± 26	< 0.001
12 months (mm Hg)	142 ± 22	145 ± 22	146 ± 19	156 ± 38	NS
Diastolic pressure					
3 months (mm Hg)	91 ± 13	95 ± 14	100 ± 13	104 ± 14	< 0.001
12 months (mm Hg)	90 ± 13	93 ± 14	93 ± 13	98 ± 19	< 0.05

FIGURES

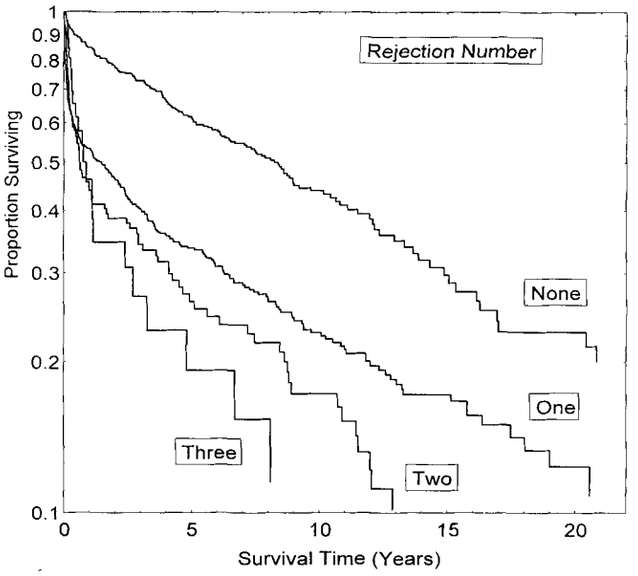

Fig. 1 Influence of rejection number on overall graft survival. Grafts with primary non-function excluded. $P < 0.001$

more than one rejection episode during the first year (Fig. 2 B). This situation arose only in 2.7% of grafts surviving 1 year. A Cox proportional hazards analysis, which only included creatinine clearance at 1 year and rejection number, showed no significant overall independent effect of rejection number on prognosis after adjustment for creatinine clearance.

The first rejection occurred at a median of 10 days after transplantation (interquartile range 7–26), the second 41 (27–56) and the third 68 (50–105). The timing of the first rejection had a significant effect on creatinine clearance at 1 year (1–7 days, 56.2 ± 20.7 ml/min; 8–60 days, 48.7 ± 21.5; > 60 days, 44.6 ± 23.7, $P < 0.02$). The timing of the second rejection had no influence on residual creatinine clearance (9–30 days, 47.8 ± 23.9 ml/min; 31–60, 48.3 ± 21.4; 60–300, 49.5 ± 21.6, not significant). Patients experiencing their first rejection more than 2 months after transplantation had a poorer prognosis (Fig. 3 A). This was also true if patients experiencing more than one rejection were excluded ($P < 0.05$). Only four patients had both a late first rejection and more than one rejection, so survival in this group could not be analysed. Patients experiencing their second rejection more than 2 months after transplantation had, on the other hand, a better prognosis ($P < 0.01$). However, these patients had, a priori, a better prognosis by the very fact of their having already survived 2 months. When the analysis was repeated using survival time after the second episode rather than over-

Table 2 Causes of death, with graft function related to number of rejection episodes. Percentage in brackets

Cause of death	Number of rejections	
	0–1	2–3
Cardiac	45 (23)	12 (29)
Atherosclerosis	22 (11)	7 (17)
Infection	47 (24)	10 (24)
Cancer	37 (19)	3 (7)
Uraemia	10 (5)	3 (7)
Other	37 (19)	7 (17)
Total	198	42

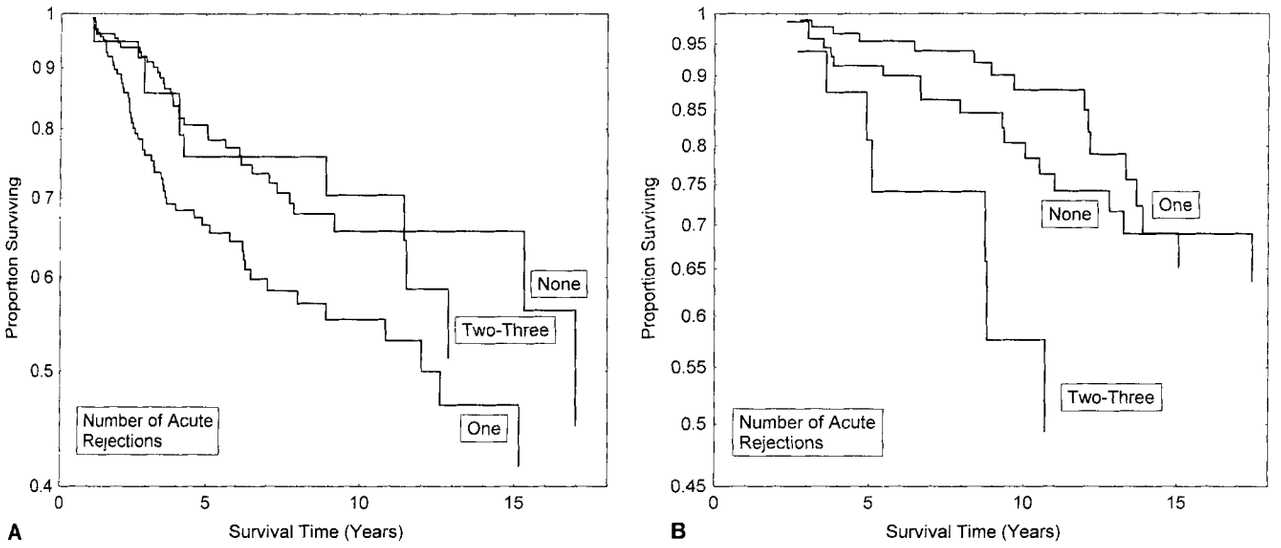

Fig. 2 A, B Influence of rejection number on graft survival (censored for patient death) stratified according to creatinine clearance at 1 year. **A** Clearance < 60 ml/min, not significant **B** Clearance > 60 ml/min, $P < 0.05$

all survival, the finding was still only borderline significant (Fig. 3 B).

Discussion

The results presented here confirm a number of previous observations. Acute rejection episodes worsen the short- and long-term prognosis for renal transplant recipients. Acute rejections were rarer with a good DR match (but not AB match in this patient group), cyclosporine treatment and with living, related donors, emphasising that the main cause of acute rejection is allogenic mismatching. The higher prednisone and azathioprine dose seen in patients experiencing rejections is probably a consequence of the rejections rather than a cause. We found no significant relationship between delayed graft function and rejection incidence; indeed in our patient group, delayed graft function and long cold ischaemia times seemed to protect against rejection. This is in contrast to the result of Troppmann et al. [18] who found delayed graft function to be a significant risk factor for rejection.

We found an increased mortality in patients with two or more rejection episodes. This is not surprising since these patients were treated with high doses of immunosuppressive drugs. There was, however, no evidence of increased cancer incidence and death due to infection was only marginally increased. The main cause of the excess mortality was atherosclerotic complications, presumably secondary to excessive steroid therapy.

We chose to analyse the influence of graft function at 1 year for three reasons: (a) graft survival curves change shape at approximately 1 year from an exponential function to a log-linear function, suggesting the existence of two different disease processes; (b) acute rejection is rare after 1 year; in this study 97 % of all biopsy-verified acute rejections occurred within 1 year; and (c) loss due to chronic renal allograft dysfunction is rare before 1 year. Most of the deleterious long-term influences of acute rejections could be accounted for by graft dysfunction at 1 year. Only in patients maintaining a good graft function (> 60 ml/min) despite two or more rejection episodes (a fairly rare event, occurring in less than 3 % of cases), could an independent long-term negative impact of rejection be demonstrated. Thus, some chronic graft loss must necessarily have an immunological aetiology. On the other hand, the present study is compatible with the theory that most of the long-term damage caused by rejections is caused by initial, irreversible graft tissue destruction at the time of rejection, followed by non-immunological chronic injury in hypofunctioning kidneys.

Patients experiencing late (> 2 months) initial rejection had a poor prognosis. This has been described by others [19, 20]. Matas [19] originally described the same phenomenon. In a later publication [2], this was modified; late initial episodes had a better prognosis than early episodes if single episodes were compared, and worse if multiple episodes were compared. We were only able to do a subgroup analysis for patients with single episodes and found, as before, that late rejection carries the worst prognosis, a finding that is supported by most of the current literature. Since these patients also had the lowest graft function at 1 year, the explanation for their poor prognosis is probably that they suffer more severe rejections, with increased graft destruction, enabling later, haemoynamically mediated damage to occur.

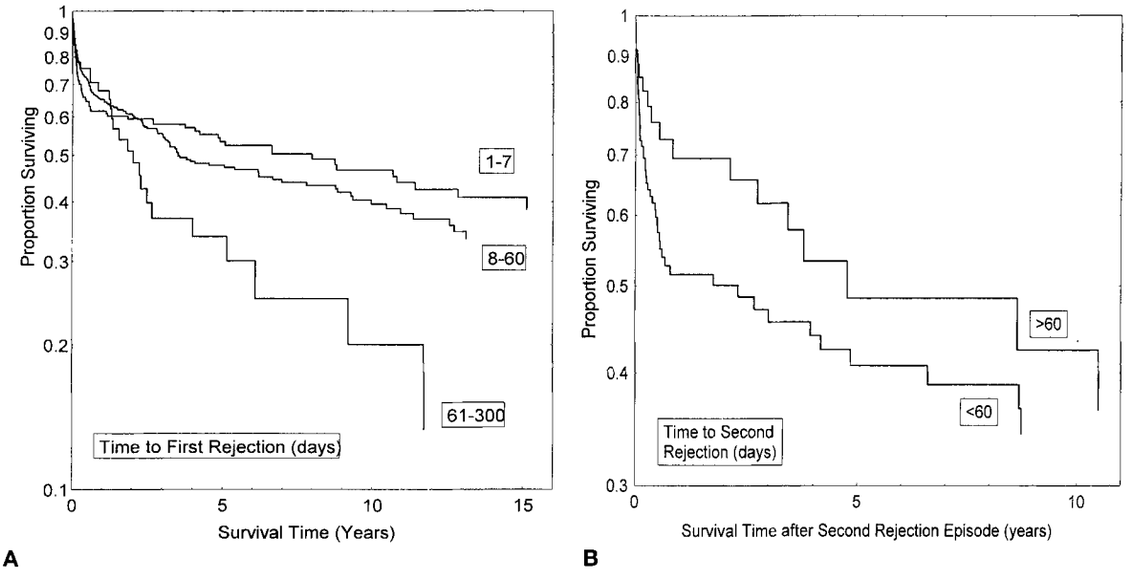

Fig. 3 A, B Influence of time to rejection episode on graft prognosis (censored for patient death). **A** Graft survival and time to first rejection, $p < 0.05$ (late rejection group versus others, $p < 0.01$). **B** Graft survival after second rejection, $p = 0.07$

In contrast, we found a significantly better prognosis in patients with a late second rejection. This has not previously been described. This finding was partly explained by the fact that these patients had had a graft survival for more than 2 months but, after correction for this, there was still a borderline significant tendency for better survival. Graft function at 1 year was similar in the two groups. This finding should be confirmed by other studies but at present there is no reason to assume that late second rejection episodes, providing they occur within the first year, have any negative impact compared with early second rejections.

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