

Acute rejection in kidney grafts with delayed onset of graft function

A duplex-Doppler study

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Abstract. Forty-five kidney transplant recipients with delayed onset of diuresis due to acute tubular necrosis (ATN) were examined with duplex ultrasonography (DU). Resistive index (RI) was measured on the 4th post-transplant day. Eleven grafts (24%) developed acute rejection. Mean RI prior to rejection of the 4th postoperative day in these grafts was 0.97 and in the 34 grafts which did not develop rejection mean RI was 0.82. There were 2/26 rejections (8%) in the group of grafts with an initial RI below 0.9 and 9/19 rejections (47%) in the group of grafts with RI of 0.9 or above on the 4th post-transplant day. Six months postoperatively there were 2/26 nonfunctioning grafts in the group with lower initial RI values (< 0.9) and 6/19 nonfunctioning grafts in the group with higher indices (≥ 0.9). In nonfunctioning grafts a high initial RI (≥ 0.9) indicates that these grafts will be prone to developing acute rejection.

Key words: Duplex-Doppler, in kidney transplantation – Rejection, acute, kidney, duplex-Doppler – Kidney transplantation, duplex-Doppler, rejection

The most common reason for delayed onset of diuresis after renal transplantation is acute tubular necrosis (ATN). The factors behind ATN may be prolonged cold ischaemia, improper management of the donor, suboptimal storage of the graft, immunological properties of the recipient and management of the recipient and the donor during and after operation. The identification of an acute rejection in a nonfunctioning graft constitutes a diagnostic problem because of the lack of certain clinical signs such as decrease in urine output and increase in serum creatinine values [2, 11]. Former studies have showed that duplex ultrasonography cannot distinguish ATN from rejection [3, 5, 8, 12]. However, it has been suggested that the ATN grafts which additionally develop rejection have a higher vascular impedance than those that do not [1].

Our purpose in the present study was (1) to measure resistive index (RI) values with duplex ultrasonography in grafts which are nonfunctioning due to ATN, (2) to find out if there is any difference between the RI in those nonfunctioning grafts which develop acute rejection and those which do not, and (3) to evaluate the prognostic value of RI in regard to the later outcome of the graft.

Materials and methods

Forty-five renal transplant recipients with delayed onset of graft function were included in this study. The transplantations were performed between May 1988 and July 1989. All grafts were cadaveric. The cold ischaemia time (CIT) ranged from 17 h to 46 h. Seven grafts had a CIT below 24 h, 26 grafts a CIT of 24–36 h and 12 grafts a CIT of more than 36 h. Donor age ranged from 14 to 60 years. Twenty-eight recipients (62%) had a primary kidney disease. 11 (24%) had diabetic nephropathy, 3 (7%) had polycystic degeneration, 2 (4%) hydronephrosis and 1 (2%) amyloidosis. The age of the recipients ranged from 22 to 63 years. Seventeen were female and 28 male. All recipients were on dialysis before transplantation; the dialysis time ranged from 2 months to 9 years. Nine recipients had had previous kidney transplantations. The present transplantation was the second for six recipients, the third for two recipients and the fourth for one recipient.

Delayed onset of graft function was defined by the need for post-operative dialysis. Diagnosis of acute rejection was based on clinical signs and confirmed by fine-needle aspiration biopsy. The result of biopsy was expressed by a TCI score (total corrective increment score), which quantifies the immunological activity in the graft. TCI values of less than 3 are considered normal [4].

Duplex-Doppler ultrasonography was routinely performed on the 3rd or 4th post-transplant day, and additionally on demand. A Toshiba SSA 100L scanner with 3.5-MHz duplex probe was used for imaging. Doppler spectra were recorded from the segmental branches of the main transplant artery, from interlobar and arcuate arteries. Resistive index (RI) was measured for each spectrum using a formula:

$$RI = (V_{sys} - V_{dias}) / V_{sys}$$

in which V_{sys} is peak systolic velocity and V_{dias} maximum end-diastolic velocity. It has been shown earlier that although pulsatility slightly decreases as one proceeds distally in the arterial tree, there is no statistical difference in RI values obtained from different arterial sites [6]. Like previous authors we used an average value of RI [1, 3, 6]. The maximum value of RI was 1.0, indicating a diastolic block. An RI equal to 0.9 was selected as the cut-off point for pathological vas-

Table 1. Resistive index, dialysis time, serum creatinine levels and outcome in 45 patients with delayed onset of graft function. ATN-NOR, grafts without rejection; ATN-REJ, grafts with rejection; RI, resistive index

	RI day 4 after transplant	Dialysis time after transplant (days)	Serum creatinine levels			Outcome at 6 months
			Days 14–21 after transpl. ($\mu\text{mol/l}$)	3 Months after transpl. ($\mu\text{mol/l}$)	6 Months after transpl. ($\mu\text{mol/l}$)	
ATN-NOR	Mean 0.82 SD 0.12	Mean 10.6 SD 5.3 ($n = 31$)	Mean 249 SD 106 ($n = 32$)	Mean 149 SD 49 ($n = 25$)	Mean 129 SD 52 ($n = 20$)	Functioning: 28/34 Nonfunctioning :3/34 Dead: 3/34
ATN-REJ	Mean 0.97 SD 0.08	Mean 17.7 SD 12.5 ($n = 9$)	Mean 243 SD 83 ($n = 9$)	Mean 235 SD 215 ($n = 7$)	Mean 146 SD 51 ($n = 7$)	Functioning: 7/11 Nonfunctioning 4/11

Table 2. Prognostic value of RI in regard to acute rejection and graft function. PPV, Positive predictive value; NPV, negative predictive value

	RI < 0.9	RI \geq 0.9	
No. of patients	26	19	Sensitivity 0.82 Specificity 0.71
Acute rejections	2 (7.7%)	9 (47%)	PPV 0.47 NPV 0.92
Outcome at 6 months	22 with function (85%) 2 in dialysis (7.7%) 2 dead (7.7%; died with functioning grafts)	13 with function (68%) 6 in dialysis (32%)	

cular resistance. The RI values were correlated with the TCI values from the biopsies obtained on the 4th post-transplant day.

Mann-Whitney and Fisher's exact tests were used in statistical analysis. A significance level of 5% was used. Sensitivity, specificity and positive and negative predictive values were calculated for RI in regard to a subsequent acute rejection.

Results

Among the 45 grafts with delayed onset of diuresis there were 11 grafts (24%) which developed an acute rejection (ATN-REJ group). In 34 grafts no rejection occurred during the post-transplant period (ATN-NOR group). These groups did not differ significantly as to donor age, histocompatibility or CIT. The mean pre-transplant dialysis time was longer in the ATN-REJ group (2.7 years) than in ATN-NOR group (1.7 years), but the difference turned out to be statistically insignificant.

Patients in the ATN-REJ group had higher levels of panel reactive antibodies (PRA) prior to transplantation than patients in the ATN-NOR group, but the difference was statistically insignificant ($P = 0.08$, Mann-Whitney test). Rejections occurred on the 4th to 29th post-transplant days (mean 10.6 days); nine rejections occurred before the 12th post-transplant day, one on the 20th and one on the 29th post-transplant day. In all cases the initial duplex ultrasonography was performed prior to the rejection episode.

The mean dialysis time after transplantation was 10.6 days in the ATN-NOR group and 17.7 days in the ATN-REJ group.

The mean RI on the 4th post-transplant day in the ATN-NOR group was 0.82 (2 SD 0.23, SE 0.02) and in the

ATN-REJ group it was 0.97 (2 SD 0.17, SE 0.03); the difference is statistically significant ($P = 0.0007$, Mann-Whitney test). Nine grafts out of 11 in the ATN-REJ group had the maximum RI (1.0) and two had less than 0.9 (0.87 and 0.74). The two grafts which developed rejection on the 20th and 29th post-transplant days underwent additional duplex ultrasonography 2 weeks after transplantation. The former had an RI of 1.0 on both the 4th and the 14th post-transplant day, while the latter had RI values of 0.74 and 0.68 respectively.

In the ATN-NOR group the RI in five out of 34 grafts was 1.0, in five it was between 0.9 and 0.99 and in 24 grafts it was less than 0.9.

The TCI score on the 4th day ranged from 0.2 to 4.8 (mean 1.7) in the ATN-NOR group and from 0.3 to 5.5 (mean 2.7) in the ATN-REJ group. The difference was not statistically significant ($P = 0.07$, Mann-Whitney test).

Six months after transplantation there were 28 functioning grafts out of an initial 34 in the ATN-NOR group, three patients were on dialysis and three had died. In the ATN-REJ group seven out of 11 grafts were functioning and four patients were on dialysis.

There was no significant difference between the study groups in regard to serum creatinine levels at the time of discharge from the hospital and 3 and 6 months after transplantation (Table 1).

The study population was additionally divided into two different groups, those with an RI below 0.9 ($n = 26$) on the 4th post-transplant day and those with an RI of 0.9 or above ($n = 19$). In the group with an RI below 0.9 there were 2/26 rejections and in the group with an RI of 0.9 or above rejections occurred in 9/19 grafts. The difference is statistically significant ($P = 0.003$, Fisher's exact test). The sensitivity of RI in predicting subsequent rejection was 0.82 and the specificity was 0.71. The positive predictive value was 0.47 and the negative predictive value 0.92. Six months after transplantation 22 of the 26 grafts (85%) with lower initial RIs were functioning (two patients were on dialysis and two had died with functioning grafts). Thirteen of the 19 grafts (68%) with higher RIs were functioning after 6 months (Table 2).

Discussion

After kidney transplantation an acute allograft rejection may be particularly insidious in cases with delayed onset of diuresis. Fine-needle aspiration biopsies or core biop-

sies are needed to detect immunological activity in the graft [4, 9]. Radionuclide studies with technetium-99m-DTPA may be of value in the differentiation between ATN and rejection: in ATN the graft shows relative preservation of perfusion compared to clearance, but in rejection perfusion is more impaired [2].

Duplex ultrasonography shows increased vascular resistance in acute rejection, but there are studies showing that grafts with ATN also have increased vascular resistance [3, 5, 8, 12].

Allen et al. [1] reported that the patients with ATN who subsequently developed acute rejection had higher indices even before rejection than those who never showed evidence of rejection. However, no statistical difference was found between these two groups in regard to RI.

In the present study a cut-off point of 0.9 for a pathological RI was used because we had found earlier that among 150 grafts, none without either ATN or acute rejection had an RI of 0.9 or above [7].

RI values in the present study differed significantly between the grafts that subsequently developed acute rejection and the grafts that did not. The reason for the higher vascular resistance can be discussed. It may be due to oedema of the graft tissue before cytologically manifest rejection and it can be detected before any inflammatory activity is seen in fine-needle aspiration biopsy.

High initial RI values seem to carry a bad prognosis: the incidence of acute rejection is higher among grafts with pathological initial RI values (≥ 0.9 , incidence 47%) than among those with RI values in the normal range (< 0.9 , incidence 8%). In our clinic the overall incidence of acute rejection during the first post-transplant month between 1987 and 1989 has been 25% [10]. Of course, the prognostic value of a high initial RI in regard to the later course of the graft is questionable, but the 6-month graft survival rate was higher in grafts with low RI values than in those with pathological RI values.

Conclusion

Patients with a late onset of renal transplant function should undergo duplex-Doppler examination during the very first days after transplantation. Fine-needle aspiration biopsy is the cornerstone in the diagnosis of rejection, especially during the nonfunctioning phase of the graft. This study suggests that high initial resistive index (≥ 0.9) seems to be associated with an increased probability of

acute transplant rejection during the following 1 or 2 weeks. Frequent and careful follow-up with fine-needle or core biopsies is indicated in these patients, allowing early diagnosis of an acute rejection.

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References

- Allen KS, Jokarsky DK, Arger PH, Velchik MG, Grumbach K, Coleman BG, Mintz MC, Betsch SE, Perloff LJ (1988) Renal allografts: prospective analysis of doppler sonography. *Radiology* 169: 317-376
- Delmonico FL, McKusick KA, Cosimi AB, Russell PS (1977) Differentiation between renal allograft rejection and acute tubular necrosis by renal scan. *Am J Roentgenol* 128: 625-628
- Genkins SM, Sanfilippo FP, Carroll BA (1989) Duplex doppler sonography of renal transplants: lack of sensitivity and specificity in establishing pathologic diagnosis. *Am J Roentgenol* 152: 535-539
- Häyry P, Willebrand E von (1981) Practical guidelines for fine needle aspiration biopsy of human renal allografts. *Ann Clin Res* 13: 228-231
- Rifkin MD, Needleman L, Pasto ME, Kurtz AB, Foy PM, McGlynn E, Canino C, Baltarowich OH, Pennell RG, Goldberg GG (1987) Evaluation of renal transplant rejection by duplex Doppler examination: value of resistive index. *Am J Roentgenol* 148: 759-762
- Rigsby CM, Burns PN, Weltin GG, Chen B, Bia M, Taylor KJW (1987) Doppler signal quantitation in renal allografts: comparison in normal and rejecting transplants, with pathologic correlation. *Radiology* 162: 39-42
- Saarinen O (1990) Diagnostic value of resistive index of renal transplants in the early postoperative period. *Acta Radiol* 32: 166-169
- Saarinen O, Ahonen J, Eklund B, Höckerstedt K, Isoniemi H, Salmela K, Tierala E, Willebrand E von, Edgren J (1990) Duplex ultrasound and acute rejection. *Transplant Proc* 22: 167-168
- Salmela K, Eklund B, Höckerstedt K, Pettersson E, Sarparanta T, Willebrand E von, Ahonen J (1986) Rejection and early non-function in renal allografts. *Transplant Proc* 18: 77-79
- Salmela K, Willebrand E von, Kyllönen L, Koskimies S, Isoniemi H, Eklund B, Höckerstedt K, Ahonen J (1991) The association of HLA-DR antigens with acute steroid-resistant rejection and poor kidney graft survival. *Transplantation* 51: 768-771
- Shanahan WSM, Klingensmith WC, Weil R (1981) ^{99m}Tc -DTPA renal studies for acute tubular necrosis: specificity for dissociation between perfusion and clearance. *Am J Roentgenol* 136: 249-253
- Warshauer DM, Taylor KJW, Bia MJ, Marks WH, Weltin GG, Rigsby CM, True LD, Lorber MI (1988) Unusual causes of increased vascular impedance in renal transplants: duplex doppler evaluation. *Radiology* 169: 367-370