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RECURRENCE OF TYPE I MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS AFTER RENAL TRANSPLANTATION

ANALYSIS OF THE INCIDENCE, RISK FACTORS, AND IMPACT ON GRAFT SURVIVAL

MARGRET B. ANDRESDOTTIR,^{1,2} KAREL J.M. ASSMANN, ANDRIES J. HOITSMA, ROBERT A.P. KOENE,
 AND JACK F.M. WETZELS

Division of Nephrology and Department of Pathology, University Hospital Nijmegen, 6500 HB Nijmegen, The Netherlands

Background. The information in the medical literature on the incidence of recurrence of type I membranoproliferative glomerulonephritis (MPGN) after renal transplantation and its impact on graft survival is limited because most data are derived from case reports or from studies involving a small number of patients.

¹ M.B. Andresdottir is supported by a grant from the Dutch Kidney Foundation (C96.1543).

² Address correspondence to: M.B. Andresdottir, Department of Medicine, Division of Nephrology, University Hospital Nijmegen, P.O. BOX 9101, 6500 HB Nijmegen, The Netherlands.

Methods. We analyzed the data from our transplant center. Among 1097 adult patients receiving their first allograft between 1977 and 1994, we identified 32 patients with type I MPGN.

Results. A recurrence was detected in 9 of the 27 recipients of a first cadaveric graft (33%). The cumulative incidence reached 48% at 4 years after transplantation when patients with graft failure from other causes were censored. All patients with recurrent MPGN had clinically significant proteinuria (>1 g/24 hr) that was first observed at a median time of 20 months (range, 1.5-42 months) after transplantation. Graft survival was significantly worse in patients with

recurrence as compared with patients without recurrence. Mean duration of graft survival after the diagnosis of recurrence was 40 months. We could not detect any clinical characteristics of patients or donors that were associated with recurrent disease. However, an increased risk of recurrence was observed in patients with the HLA haplotype B8DR3. Four patients received an HLA-identical graft from a living related donor. Recurrence occurred in three patients (75%), with ensuing graft loss in two. The only patient with a haploidentical living related graft did not have a recurrence. Five patients with a recurrence in the first graft received a second transplant. Recurrence was observed in four of these patients (80%).

Conclusions. Type I MPGN recurred after renal transplantation in half of the patients. The incidence may be even higher in recipients of an identical living related donor graft and in patients receiving a second transplant after having experienced a recurrence in their first graft. Recurrence of type I MPGN has a detrimental effect on graft survival.

Type I membranoproliferative glomerulonephritis (MPGN,* alternatively named mesangiocapillary glomerulonephritis) is a rather uncommon form of glomerulonephritis. In most patients, the disease runs a progressive course toward end-stage renal failure, necessitating dialysis or kidney transplantation (1). Transplant recipients with type I MPGN can experience a recurrence of the original disease in their allograft. The incidence of recurrence of type I MPGN has been reported to be as low as 9% and as high as 53% (2, 3). It is difficult to reconcile data in the literature, since most data are derived from case reports or from series involving a small number of patients.

We have studied the clinical course of 32 adult patients with type I MPGN who received a renal transplant in our center. In our study, we have specifically addressed the cumulative incidence of recurrent type I MPGN among the recipients of cadaveric and living related donor grafts, the influence of recurrence on graft survival, and possible risk factors associated with recurrence.

PATIENTS AND METHODS

From all adult patients (age >14 years) who received transplants in the period between August 1977 and September 1994, we identified all known patients with type I MPGN. Whenever possible, the histology of the original renal biopsies was revised.

During the study period, the following immunosuppressive drug regimens were used: from 1977 to 1983 all patients were treated with prednisone (25 mg/day for 1 month, tapered to 10 mg/day after 4 months) and azathioprine (3 mg/kg/day). From 1983 to 1985 patients were treated in a randomized study with either cyclosporine (CsA; starting with 17.5 mg/kg/day and tapering to 5 mg/kg/day at 3 months) and prednisone for the first 3 months followed by conversion to azathioprine and prednisone thereafter, or azathioprine and prednisone for the whole period (4). From 1985 to 1989 all patients received CsA and prednisone during the first 3 months and azathioprine and prednisone thereafter. In the period from 1989 to 1992, patients were treated with CsA (starting with 12 mg/kg/day and tapering to 4 mg/kg/day at 3 months) and prednisone for the first 3 months and thereafter randomized for continued treatment with either azathioprine and prednisone or CsA monotherapy (5). Since 1992, the combination of CsA and prednisone has been the cornerstone of the immunosuppressive therapy.

* Abbreviations: CsA, cyclosporine; MPGN, membranoproliferative glomerulonephritis.

All patients were followed after transplantation at regular intervals (weekly for the first 4 months, every 2–4 weeks thereafter, and from 1 year on at least every 3 months). At each visit, blood pressure, serum creatinine level, and urinary protein level were recorded. Throughout the study period, the criteria for performing a renal allograft biopsy were proteinuria (>2 g/24 hr) or a decrease in renal function.

For the purpose of this study, the medical records of all patients with type I MPGN were analyzed. The following data were documented for each patient: gender, age at diagnosis of the original disease (defined as the time of the first renal biopsy), time from diagnosis to end-stage renal failure, HLA tissue typing of donor and recipient, age at transplantation, donor source and gender, post-transplant immunosuppressive therapy, occurrence of acute tubular necrosis, and occurrence of rejection episodes. Clinically significant proteinuria (>1 g/day) heralded recurrence in all cases. Therefore, the date of onset of proteinuria was recorded and used as the date of onset of the recurrent disease.

The light microscopic changes of type I MPGN can be identical to those of chronic transplant glomerulopathy. Therefore, a definitive diagnosis of recurrent type I MPGN was made when the following biopsy criteria were fulfilled: (1) predominant deposition of C3 rather than IgM in the glomerular capillary wall on IF and (2) dense subendothelial deposits on electron microscopy (6).

Statistical analyses. Dichotomous variables were analyzed by chi-square or Mantel-Haenszel test. For continuous parameters, comparisons were made with the unpaired Student's *t* test (parametric) or the Mann-Whitney *U* test (nonparametric variables). Survival probabilities were calculated with the Kaplan-Meier method, and the log-rank test was used for comparison of survival curves. A *P*-value of <0.05 was considered to be statistically significant. Unless otherwise noted, values are given as mean ± SD.

RESULTS

Among the 1097 adult patients receiving their first renal allograft, there were 463 patients with suspected glomerulonephritis/glomerulopathy (42%). In 118 patients, glomerulonephritis/glomerulopathy was secondary to systemic diseases, such as amyloidosis, diabetes mellitus, or systemic lupus erythematosus. In the 345 patients with a probable diagnosis of primary glomerulonephritis, a histological diagnosis was available in 61%. In this group, we identified 32 patients with type I MPGN as their original renal disease (15% of biopsy-proven cases of glomerulonephritis). The histological diagnosis of the original kidney disease could be revised and confirmed in 26 patients. No tissue from the native kidney was available for examination in the remaining six patients, but the available descriptions of the histology and the clinical characteristics of the patients were compatible with the diagnosis of type I MPGN. The clinical characteristics of the 32 patients with type I MPGN are given in Table 1. We analyzed the data according to donor source.

TABLE 1. Clinical characteristics of patients with type I MPGN^a

| | |
|------------------------------|-------|
| Sex (M/F) | 22/10 |
| Age at diagnosis (yr) | 25±9 |
| Interval diagnosis-ESRD (mo) | 62±44 |
| Age at transplantation (yr) | 31±8 |
| Donor source | |
| Cadaver | 27 |
| LRD, identical | 4 |
| LRD, haploidentical | 1 |

^a Abbreviations used in table: ESRD, end-stage renal disease; LRD, living related donor.

Recipients of cadaveric grafts. Twenty-seven patients were recipients of a first cadaveric graft. The average follow-up was 59 months (range, 0.3–192 months). In the patients with graft loss, follow-up was terminated at the time of graft failure. Six patients lost their grafts within 9 months after transplantation. The follow-up of the remaining patients was at least 12 months.

A recurrence was diagnosed in nine patients (33%); when patients with graft failure from other causes were censored, the cumulative incidence of recurrence reached 48% at 4 years after transplantation (Fig. 1). Proteinuria of >1 g/day was detected at a median of 20 months after transplantation (range, 1.5–42 months; Fig. 1) and progressed to the nephrotic range in all but one patient (with the shortest follow-up of only 1 year). In two patients with a recurrence, deterioration of renal function coincided with the onset of proteinuria. In the remaining seven patients, renal function was stable at the onset of proteinuria. In six of these patients, there was a significant and progressive increase of serum creatinine at a median time of 16 months (range, 12–30 months) after the onset of the clinical recurrence. Renal function remained stable in only one patient, who died from septicemia at 10 years after onset of proteinuria. Of the nine patients with recurrence, thus far seven have lost their kidneys, and the mean period of survival after the appearance of proteinuria was 40 months. Recurrence was the main cause of graft loss in five patients. One patient had a concomitant chronic vascular rejection and one patient died of septicemia with good renal function. At present, there are only two patients with functioning grafts; their serum creatinine levels are 225 and 351 $\mu\text{mol/L}$ at 1 year and 4.5 years, respectively, after transplantation.

To analyze the impact of recurrent type I MPGN on graft survival, we compared graft survival of patients with recurrence and without recurrence, thereby excluding the above-mentioned six patients with early graft loss. Graft survival was significantly worse in patients with recurrence ($P < 0.05$, Fig. 2).

For the analysis of risk factors, we divided the patients into three groups: a group with proven recurrence, a group without recurrence (and a follow-up of >1 year), and a group

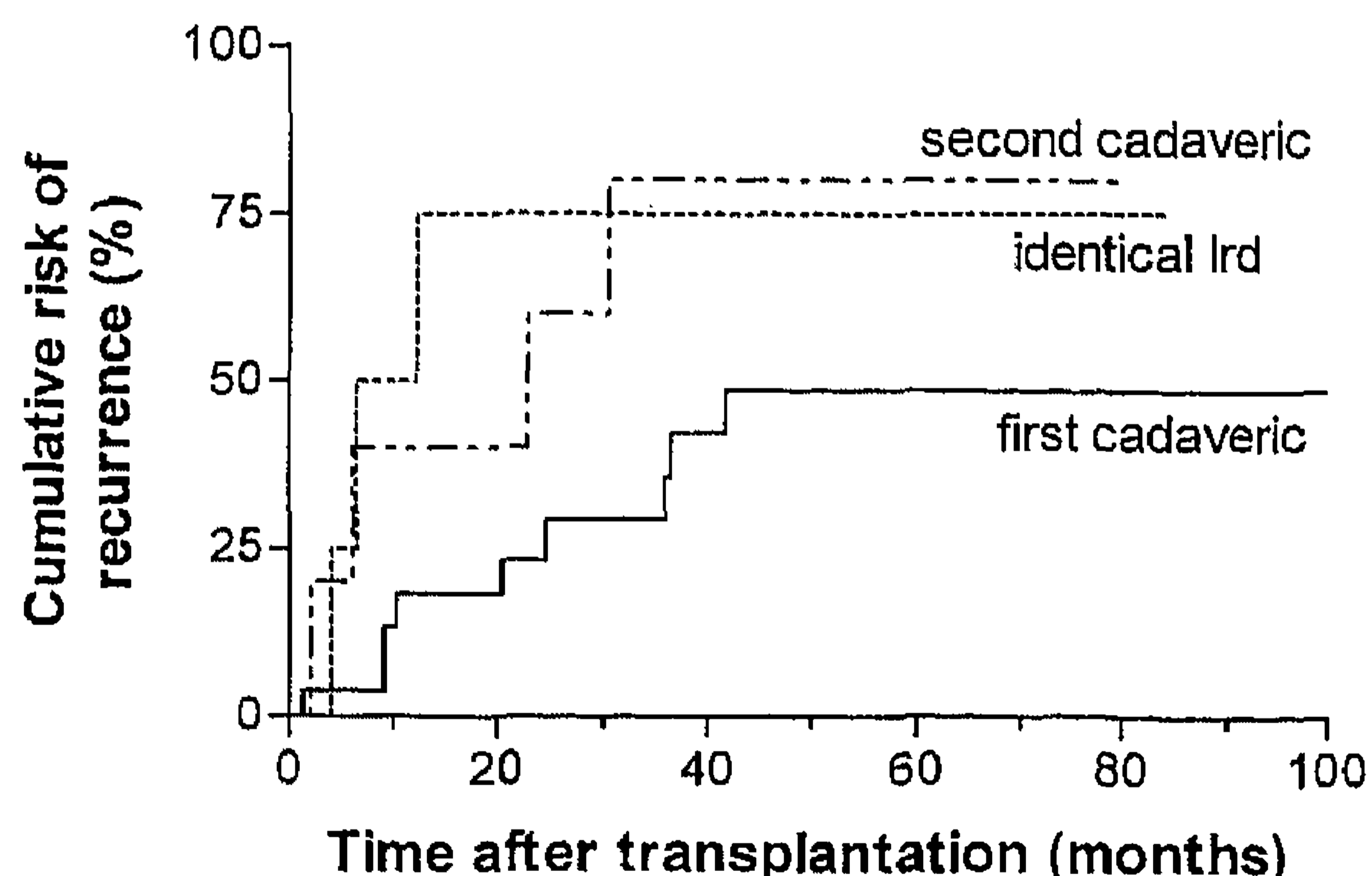


FIGURE 1. The cumulative risk of recurrence of type I MPGN after renal transplantation in patients who received a cadaveric donor graft (—), in recipients of an identical living related donor (lrd) graft (---), and in patients with a second transplant after having experienced recurrence in the first one (- - -). In the first group, five patients have survived without evidence of recurrence for more than 100 months after transplantation (range, 144–192 months).

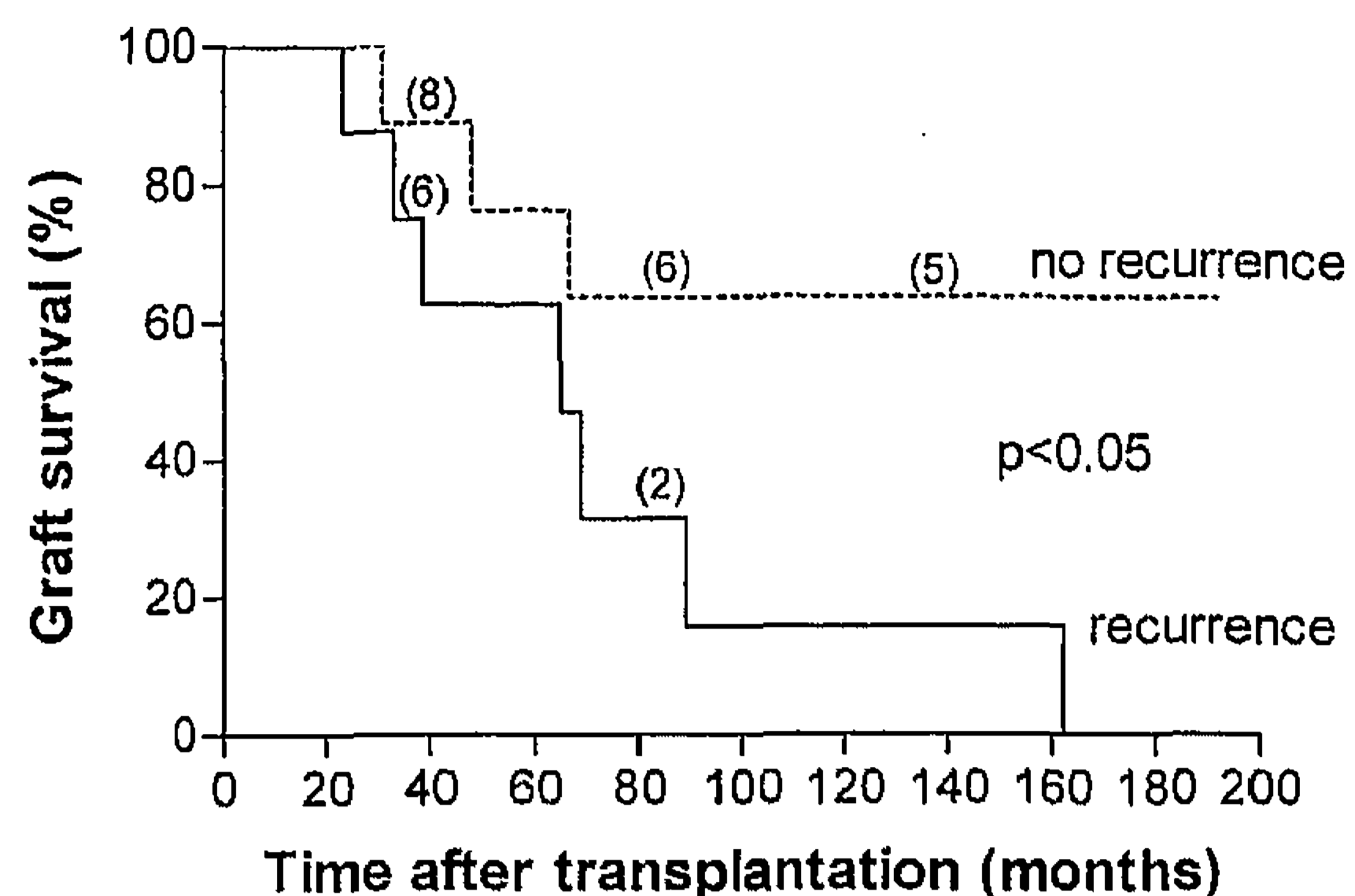


FIGURE 2. Graft survival in patients with (—) and without (---) recurrence, $P < 0.05$. Number in brackets indicates the number of patients at risk.

with no evidence of recurrence but early graft loss (within 9 months). Table 2 shows the characteristics of these patient groups. Sex, age at diagnosis, and the rate of progression of the original disease were not associated with the risk of recurrence. Also donor characteristics and the use of certain immunosuppressive regimens were not predictive. The only risk factor we identified was an HLA haplotype. The haplotype HLA B8DR3 was associated with a higher risk of recurrence; 5 out of 9 patients with recurrence had this haplotype, compared with 1 out of 11 patients without recurrence ($P < 0.05$).

In the study period, complement levels were not routinely measured after transplantation. From the medical records we obtained information on complement levels from seven patients with recurrence and from four patients without recurrence. In these patients, at least one measurement of C3 was available before transplantation and one (>2 months) after transplantation. In the group with recurrence, four patients had a normal C3 before and after transplantation. Three patients had low C3 levels before transplantation, and these patients remained hypocomplementemic after transplantation. On the other hand, the four patients without recurrence were hypocomplementemic before transplantation, and their C3 levels normalized within 2 months after transplantation.

Recipients of grafts from living related donors. The risk of recurrence appeared higher in the patients who received an HLA-identical graft from a living donor, with recurrence in three of the four patients (75%). The onset of proteinuria was earlier than in the recipients of cadaveric grafts, occurring at 4, 6.5, and 12 months (Fig. 1). Two patients lost their grafts as a consequence of the recurrence at 4.5 and 5.5 years after transplantation. One patient has a functioning graft with a serum creatinine level of 116 $\mu\text{mol/L}$ at 1 year after transplantation. None of the recipients of HLA-identical living related donor grafts had the HLA B8DR3 haplotype. The only patient with a haploidentical living related donor did not have a recurrence of type I MPGN.

Second transplantation. Five patients who lost their first graft due to recurrence received a second transplant. Recurrence occurred in four of them (80%) at 6, 12, 26, and 30 months after transplantation (Fig. 1). Recurrence caused graft failure in three of these four patients, and the remaining patient has deteriorating kidney function 3 years after transplantation. The only patient without a second recur-

TABLE 2. Characteristics of patients with and without recurrent type I MPGN after first cadaveric transplantation^a

| | With recurrence (n=9) | Early graft loss (n=6) | No recurrence (n=12) | P |
|------------------------------------|--------------------------|---------------------------|-------------------------|-------|
| Sex (M/F) | 4/5 | 3/3 | 10/2 | NS |
| Age at diagnosis (yr) | 28±9 | 21±6 | 24±10 | NS |
| Interval diagnosis-ESRD (mo) | 53±40 | 64±63 | 63±40 | NS |
| Age at transplantation (yr) | 35±10 | 27±5 | 32±8 | NS |
| Donor age (yr) | 34±13 | 36±18 | 37±15 | NS |
| Donor sex (M/F) | 6/3 | 2/4 | 4/8 | NS |
| HLA mismatch | 1.8 | 1.8 | 2.0 | NS |
| HLA B8DR3 ^b | 5 | 2 | 1 | <0.05 |
| ATN (n) | 2 | 2 | 3 | NS |
| Therapy after transplant | | | | |
| AZA/prednisone | 5 | 2 | 5 | NS |
| CsA/prednisone | 4 | 4 | 7 | NS |
| Rejection (patients) | 5 | 5 | 6 | NS |
| No. of patients with graft failure | 7 | 6 | 3 | |

^a Comparisons between groups were done with the Kruskal-Wallis or Mantel-Haenszel test when appropriate. Values are given as mean ± SD. Abbreviations used in table: AZA, azathioprine; ESRD, end-stage renal disease; ATN, acute tubular necrosis.

^b The DR haplotype was unknown in one patient in the group without recurrence and in one patient in the group with an early graft loss.

TABLE 3. Overview of the literature on recurrent type I MPGN in renal transplants

| Authors (Ref) | No. of transplant recipients with type I MPGN | No. of patients with recurrence | Rate of recurrence (%) | 95% CI ^a |
|-----------------------|--|------------------------------------|---------------------------|---------------------|
| Mathew et al. (27) | 11 | 2 | 18 | 0.02-0.52 |
| Berthoux et al. (14) | 11 | 4 | 36 | 0.11-0.69 |
| McLean et al. (15) | 16 | 7 | 44 | 0.20-0.70 |
| Hamburger et al. (28) | 40 | 7 | 18 | 0.07-0.33 |
| Curtis et al. (29) | 4 | 1 | 25 | 0.01-0.81 |
| Cameron et al. (2) | 11 | 1 | 9 | 0.0-0.41 |
| Morzycka et al. (19) | 16 | 6 | 38 | 0.15-0.65 |
| Moritz et al. (26) | 8 | 1 | 13 | 0.0-0.53 |
| O'Meara et al. (3) | 15 | 8 | 53 | 0.27-0.79 |
| Vangelista et al. (7) | 15 | 4 | 27 | 0.08-0.55 |
| Present study | 32 | 12 | 38 | 0.21-0.56 |
| Total | 179 | 53 | 30 | 0.23-0.37 |

^a Abbreviation used in table: CI, confidence interval.

rence has retained good graft function 6 years after transplantation.

Two of the patients without recurrence in the first graft (and graft survival >1 year) lost their grafts because of chronic vascular rejection. Both patients have received a second transplant, one a cadaveric graft and the other a haploidentical living related donor graft. Neither of these patients has evidence of recurrent disease in the second graft at 4 and 4.5 years after transplantation.

DISCUSSION

In our study, the overall incidence of recurrence of type I MPGN in patients who received a first renal allograft from a cadaveric donor was 33%. The incidence rate in previous studies has varied from a low of 9% to a high of 53%, with an average of 30% (Table 3). However, these overall percentages are likely to underestimate the actual recurrence rate, since the incidence of recurrence increases with time. In our study, the cumulative incidence of recurrent type I MPGN was as high as 48% at 4 years after transplantation. Our data suggest that the widely referred to recurrence rate of 30% underestimates the problem.

Could our results have been biased? We believe it is unlikely that we have missed a large number of patients with

type I MPGN as original renal disease. In our center, a histological diagnosis was made in 61% of patients with suspected glomerulonephritis. This percentage compares favorably with the literature reporting 28-53% (3, 7). Moreover, most patients with type I MPGN present with clinically overt renal disease at a young age and are likely to undergo a biopsy. No tissue was available for revision in six patients, so we had to rely on the data as reported in the medical records. Since none of these patients had a recurrence of MPGN, the inclusion of these patients may have biased our study toward underestimation of the recurrence rate. If we exclude these patients, the cumulative incidence of recurrence becomes as high as 71%.

The diagnosis of recurrence was based on characteristic findings on immunofluorescence and electron microscopy (6).³ Therefore, we consider it unlikely that we have overestimated the recurrence rate in our study.

Since we used strict biopsy criteria throughout the study, all patients with recurrent MPGN had clinical signs of recurrence, i.e., proteinuria with or without renal function impair-

³ Assmann KJM, Andresdottir MB, Koene RAP, Wetzels JFM. Immunohistological and ultrastructural differences between recurrent membranoproliferative glomerulonephritis type I and chronic transplant glomerulopathy. Manuscript submitted for publication.

ment. Clinically silent recurrences could certainly have been missed. However, in three patients without clinical recurrence, a biopsy was done at 8, 10, and 30 months after transplantation because of impairment of renal function. None of these patients showed evidence of histological recurrence.

The HLA B8DR3 haplotype was associated with an increased risk of recurrence of type I MPGN. Admittedly, this finding is based on a small number of patients and is therefore suggestive but not conclusive. We are not aware of any reports on the association between certain alleles of the major histocompatibility complex and recurrence of type I MPGN. Welch et al. (8) have reported that patients with MPGN types I and III and the extended haplotype B8,DR3,SCO1,GLO2 more rapidly progress to end-stage renal disease than patients without this haplotype. Our data do not allow us to draw firm conclusions on the effect of the immunosuppressive regimen. Recurrence occurred both in patients treated with azathioprine and prednisone and in patients treated with CsA and prednisone. However, most of our CsA-treated patients received CsA only in the first 3–6 months after transplantation. Only one study has suggested that the recurrence rate of type I MPGN was lower in CsA-treated patients (9). This finding, however, has not been confirmed by others (10, 11). Recent data show an improved survival rate after transplantation in patients with glomerulonephritis since the introduction of CsA (12). It is unclear whether this improved survival is mediated in part by a lower rate of recurrence of glomerulonephritis.

For patients with type I MPGN in their native kidneys, it is known that the C3 component of complement and to a lesser extent C4 can be decreased in the course of the disease. However, C3 levels do not correlate with disease activity (1).

Berthoux (13) found that the persistence or recurrence of hypocomplementemia after transplantation was consistently followed by recurrence of the original disease. He also observed that normal levels of complements were maintained by patients who were doing well (13). McLean et al. (14), on the other hand, did not find a clear correlation between hypocomplementemia after transplantation and recurrence. Our data on complement were limited and do not allow definite conclusions. They demonstrate that persistently normal levels of C3 do not preclude the occurrence of recurrent disease. Furthermore, one might conclude that in patients with low C3 at the time of transplantation, a persistently low C3 level favors a future recurrence, whereas patients with normalizing C3 levels have a favorable prognosis.

Recurrent type I MPGN had a serious impact on allograft function. In five patients, graft loss was considered to be entirely caused by the recurrence.

In the literature, the rate of graft loss in patients with a recurrence of type I MPGN is reported to be about 30% (12, 15–17). It is not always clear, however, whether these data included only graft loss attributed entirely to the recurrence. In our study, the graft survival of patients with recurrence was poor and comparable to the outcome reported in other single-center studies. Morzycka et al. (18) observed graft loss in five of six patients with recurrence, O'Meara et al. (3) observed it in four of eight, Vangelista et al. (7) observed it in two of the four patients, and in the series by Berthoux et al. (13) all four patients with recurrence lost their allograft.

The risk of recurrence was higher in patients who received a kidney from an identical living related donor (75%). However, the difference in the recurrence rate between recipients of cadaveric and identical living related donor grafts did not reach statistical significance, possibly due to the small number of patients. It is known that patients with IgA nephropathy have a higher risk of recurrent disease when receiving a kidney from a living related donor (19–21). This information is not available for patients with type I MPGN, although two studies suggest that all forms of glomerulonephritis are more likely to occur in recipients of a living related donor graft (3, 18).

We also observed a high risk of recurrence in a second graft in patients who had experienced a recurrence in the first graft (80%). To our knowledge, this is the first report of a series of patients who received a second transplantation after having lost their first graft due to recurrent type I MPGN. There have, however, been descriptions in the literature of several patients with a recurrence in two successive transplants (13, 18, 22–25). These data strengthen our findings that patients with a recurrence in their first graft have a high risk of a second recurrence.

In summary, we found a high cumulative risk of recurrence of type I MPGN: 48% of patients with a first cadaveric graft at 4 years after transplantation, 75% of the recipients of an identical living related graft, and 80% of recipients of a second cadaveric graft who had a recurrence in their first graft. The haplotype HLA B8DR3 may be associated with recurrence in patients with cadaveric grafts. Graft survival was negatively influenced by the recurrence.

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