Risk factors and outcome of focal and segmental glomerulosclerosis recurrence in adult renal transplant recipients

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Abstract
Background. Recurrence of nephrotic syndrome (NS) after renal transplantation for primary focal segmental glomerulosclerosis (FSGS) is a frequent and still unpredictable complication. However, risk factors for recurrence have not yet been clearly identified.

Methods. Data from 33 patients who underwent 35 renal transplantations for FSGS in two French centres are reported.

Results. Recurrent NS occurred in 12 transplant recipients (34%). A significantly higher number of patients in the group with recurrence (R group) compared with the group without recurrence (NR group) received cyclosporine for FSGS treatment before transplantation (83.3% vs 43.4%, P<0.02). Donors of R group recipients were significantly older than those of the non-NR group recipients (42.8 years vs 35 years, P<0.05). A higher number of patients from the R group required post-transplantation dialysis (33.3% vs 17.4%, P=0.002). Surprisingly, acute rejection occurred more frequently in patients of the NR group compared with the R group, although the difference was not significant. Among the 12 patients with NS relapse, 9 were treated with plasmapheresis. Graft loss related to recurrence occurred in 6 cases. The 5-year graft survival was significantly lower in patients with recurrent NS compared with patients without recurrence (57% vs 82%, P<0.001).

Conclusion. This study confirms the benefit to identify in the future clinical or biological predictive risk factors for NS recurrence after renal transplantation. It also indicates that donor age is a reliable risk factor for recurrence in adult recipients and suggests for the first time a possible opposite relationship between recurrent FSGS and acute rejection.

Keywords: acute rejection; focal segmental glomerulosclerosis; recurrence; renal transplantation

Introduction

Focal segmental glomerulosclerosis (FSGS) is one of the most frequent glomerular diseases and cause of end-stage renal disease (ESRD). Recurrence of FSGS is a well-known complication after renal transplantation with reported recurrence rates of 20–80% [1–6]. The mechanisms of early proteinuria related to FSGS recurrence after transplantation are still unclear. The immediate reappearance of proteinuria after transplantation suggests that a non-dialysable circulating factor may be present, altering the glomerular permeability of renal graft [7]. Previous data suggest that this putative circulating factor which has not yet been identified could result from a systemic disorder of T cell function [8,9]. Recurrent FSGS is classically associated with an increased incidence of delayed graft function and acute rejection and results in graft loss in more than 50% of transplant patients [10,11]. Treatments of FSGS recurrence, including cyclosporine therapy [12], plasma exchange and plasma protein immunoadsorption remain controversial [2,13–15].

Attempts to identify risk factors for recurrent FSGS have yielded conflicting results. Known contributors include rapid progression to end-stage renal failure [3,6,16–18], young age of onset of FSGS [1,19], presence of mesangial proliferation on initial renal biopsy [16,18,20], use of immunosuppressive therapy [4,21] and loss of a previous graft from recurrent disease [6,13,16]. Since Hoyer et al. [22] in 1972 first reported
recurrence of nephrotic syndrome (NS) associated with the development of FSGS in renal allograft, many authors have described potential risk factors and therapeutic approaches. However, most reports involved paediatric recipients. This study was designed to retrospectively analyse the clinical course and the risk factors for FSGS in a cohort of adult recipients followed in two transplant centres.

Subjects and methods

From January 1986 to December 2001, 1203 renal transplantations were performed in two transplant centres (Henri Mondor hospital, Créteil and Hopitaux Universitaires, Strasbourg, France). During this period, 35 kidneys (2.9%) were grafted in 33 adult recipients who developed ESRD as a result of idiopathic NS related to either FSGS or minimal change disease (MCD) documented by renal biopsy. Patients with family history of NS, HIV-associated nephropathy and secondary FSGS were excluded from this study. Grafts came from 33 deceased donors and 2 living-related donors. Six patients had a second transplantation; causes of the first graft loss were recurrent NS in 3 cases and chronic rejection in the 3 others. Four patients underwent pre-transplantation bilateral nephrectomy. Acute rejection episodes were treated with intravenous methylprednisolone pulses on 3 subsequent days and with antithymocyte globulins (ATG) in cases of steroid-resistant rejections.

Patients were divided into 2 groups according to the presence (recurrent group, R group) or absence (non-recurrent group, NR group) of recurrent NS. Recurrence was defined by the reappearance of proteinuria (>3 g/24h) in the absence of acute rejection or urinary tract infection. The diagnosis of recurrent NS was confirmed by renal biopsy in all cases. Complete remission was defined by the return of urine protein to less than 0.3 g/24h. Partial remission was defined by a 50% reduction of the proteinuria. Several risk factors for recurrence were analysed, including sex and age at the onset of NS, initial FSGS treatment, rapidity of progression to renal failure, presence of a mesangial hypercellularity in native kidneys, duration of dialysis, recurrence in a previous transplantation, HLA matching, donor’s characteristics of the patients are listed in Table 1. The median delay between transplantation and recurrence of nephrotic syndrome (NS) was 22 days (IQR: 1–206 days). The recurrence was observed during the first month after renal transplantation in 8 patients and between the 2nd and the 7th month in 4 patients. Among the 8 patients with early recurrence (during the 1st month after kidney transplantation) 6 patients experienced immediate recurrence within the first 24h following transplantation.

The median delay between the onset of proteinuria and the allograft biopsy was 1.2 months (IQR: 5 days–14 months). Histological features on light microscopy consisted in MCD in 5 patients, mesangial expansion (ME) in 3 patients and typical segmental glomerulosclerosis in 4 patients. Pre-transplant characteristics of the patients are listed in Table 1. The median delay between the onset of proteinuria and the biopsy of the native kidneys was 1.8 months (IQR: 3 days–6 years). No differences were observed between the R group and the NR group in terms of gender, age at onset of FSGS diagnosis, length of progression of initial disease and duration of dialysis. A significantly higher number of patients in the R group (n = 10/12) compared with the NR group (n = 10/23), received cyclosporine for FSGS treatment before

Table 1. Demographic data of patients before kidney transplantation

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 35)</th>
<th>R group (n = 12)</th>
<th>NR group (n = 23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F</td>
<td>26/9</td>
<td>9/3</td>
<td>17/6</td>
<td>NS</td>
</tr>
<tr>
<td>Age at onset of disease (years)</td>
<td>19.9</td>
<td>17 ± 4.5</td>
<td>20 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>8.1</td>
<td>7.3 ± 2.5</td>
<td>8.5 ± 3.75</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of mesangial proliferation</td>
<td>8 (22.8%)</td>
<td>5 (41.6%)</td>
<td>3 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>3.8</td>
<td>4 ± 2.75</td>
<td>3.8 ± 2.55</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of NS</td>
<td>29 (82.8%)</td>
<td>11 (91.6%)</td>
<td>18 (78.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Microscopic haematuria</td>
<td>24 (68.5%)</td>
<td>8 (66.6%)</td>
<td>16 (69.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>10.2</td>
<td>11.1</td>
<td>9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Cyclosporine treatment before transplantation</td>
<td>20 (57.1%)</td>
<td>10 (83.3%)</td>
<td>10 (43.4%)</td>
<td>P &lt; 0.02</td>
</tr>
</tbody>
</table>

Std, mean values are reported ± standard deviation; NS, not significant.

Results

Characteristics of patients in the recurrent (R group) and the non-recurrent group (NR group)

Thirty-five renal transplantations were performed in 33 patients with FSGS. Recurrent NS developed in 12 grafted kidneys (34%) (NR group: 23 cases, 66%). Relapse occurred in all patients (3/3) who underwent a second renal transplantation after initial graft loss related to recurrent NS. The median delay between transplantation and recurrence was 22 days (IQR: 1–206 days). The recurrence was observed during the first month after renal transplantation in 8 patients and between the 2nd and the 7th month in 4 patients. Among the 8 patients with early recurrence (during the 1st month after kidney transplantation) 6 patients experienced immediate recurrence within the first 24h following transplantation.

Statistical analysis was performed using the Fischer’s exact test for categorical data and the Mann–Whitney test for non-parametric variables. The Kaplan–Meier and log-rank tests were used for description and comparison of graft survival. Values were expressed as mean ± SD or median with interquartile range (IQR) and P < 0.05 was considered statistically significant.
transplantation (83.3% vs 43.4%, \(P < 0.02\)). According to transplant centres strategy, dose of cyclosporine ranged from 2 to 5 mg/kg/day and the median duration of treatment was 14 months (IQR: 1–72 months).

A higher number of patients in the R group had mesangial hypercellularity on initial renal biopsy although this result was not statistically significant.

Characteristics of the recipients and their donors at the time of transplantation are presented in Table 2. Donors in the R group were significantly older than in the NR group (42.8 years vs 35 years, \(P < 0.05\)). No differences were observed between groups concerning age at transplantation, HLA matching and cold ischaemia time. Immunosuppressive regimen included induction therapy with steroid pulses for all patients and intravenous ATG for 23 patients, IL2 receptor antibody in 4 patients and OKT3 for 5 patients. Maintenance regimen consisted in a double therapy (prednisone and azathioprine or mycophenolate mofetil) in 1 case or a triple therapy (prednisone, azathioprine or mycophenolate mofetil, and cyclosporine A or tacrolimus) in 34 cases. Steroids were given to all patients. No statistical difference was noted between the R and the NR group. More patients from the R group required post-transplantation haemodialysis (33.3% vs 17.4%, \(P = 0.02\)). Eight patients experienced steroid-resistant acute rejection, including 3 patients in the R group and 5 in the NR group (\(P = NS\)). A trend towards a higher rate of acute rejection was observed in the NR compared with the R group (14 vs 3 patients respectively; \(P = 0.09\)). In 2 of the 3 patients from the R group, rejection occurred 10 and 30 days before recurrence and in one, 1 year after recurrent NS.

### Treatment of NS recurrence and graft outcome

Treatment and evolution of patients with recurrent NS are listed in Table 3. Among the 12 patients with NS recurrence, 9 were treated with plasma exchange associated in 1 case with immunoadsorption using sepharose bound protein A. Plasmapheresis was initiated with a median delay of 16 days after recurrence (IQR: 1–48 days). Among patients treated during the first 15 days after recurrence (\(n = 4\)), 3 patients underwent remission including complete remission in 2 cases and partial remission in 1 case. Plasmapheresis failed to induce remission in the last case. Among the 5 patients treated after 15 days, complete remission occurred in 2 patients and partial remission in 3 patients. The mean plasma exchange frequency was 1.6/week. Among the 5 patients who relapsed after the initial course of plasma exchange therapy, 3 were unsuccessfully re-treated with plasmapheresis. Finally, among the 9 patients treated with plasma exchange, 6 lost their graft because of recurrent disease. Among the 3 other patients with recurrent disease, 1 patient did not receive any specific treatment for recurrence leading to graft loss and 2 were treated with pefloxacin leading to complete remission in both cases. Pefloxacin was given at 400 mg twice daily for 2 weeks in 2 patients without any relevant adverse events. The 2 patients treated by pefloxacin did not have re-recurrence and still have stable renal function at the end of follow-up.

Overall graft survival was 97% at 1 year, 81% at 2 years and 73% at 5 years. Five-year graft survival

### Table 2. Characteristics of the FSGS recipients and their donors

<table>
<thead>
<tr>
<th></th>
<th>R group ((n = 12))</th>
<th>NR group ((n = 23))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplantation (years)</td>
<td>29.7 ± 9.2</td>
<td>33.3 ± 10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Cold ischaemia time (h)</td>
<td>24.4 ± 6</td>
<td>24.6 ± 5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Number of class 1 HLA matching</td>
<td>2.18 ± 0.57</td>
<td>2.13 ± 0.52</td>
<td>NS</td>
</tr>
<tr>
<td>Number of class 2 HLA matching</td>
<td>0.63 ± 0.18</td>
<td>0.6 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>42.8 ± 10.5</td>
<td>35 ± 8.3</td>
<td>(P &lt; 0.05)</td>
</tr>
<tr>
<td>Post-graft dialysis</td>
<td>4 (33.3%)</td>
<td>4 (17.4%)</td>
<td>(P = 0.02)</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>3 (25%)</td>
<td>14 (60.9%)</td>
<td>(P = 0.09)</td>
</tr>
</tbody>
</table>

Std, mean values are reported ± standard deviation; NS, not significant.

### Table 3. Treatment and evolution of patients with NS recurrence

<table>
<thead>
<tr>
<th>Patient</th>
<th>Proteinuria (g/day)</th>
<th>Treatment</th>
<th>Number of plasmapheresis</th>
<th>Renal graft biopsy</th>
<th>Remission</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>plasmapheresis</td>
<td>15</td>
<td>MCD</td>
<td>partial</td>
<td>Relapse-Graft loss</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>plasmapheresis</td>
<td>12</td>
<td>ME</td>
<td>complete</td>
<td>Acute rejection-Graft loss</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>plasmapheresis + IA</td>
<td>13</td>
<td>MCD</td>
<td>complete</td>
<td>Creatinine level 12 (\mu)mol/l</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>plasmapheresis</td>
<td>12</td>
<td>MCD</td>
<td>partial</td>
<td>Creatinine level 12 (\mu)mol/l</td>
</tr>
<tr>
<td>5</td>
<td>3.5</td>
<td>plasmapheresis</td>
<td>12</td>
<td>MCD</td>
<td>partial</td>
<td>Relapse-Graft loss</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>plasmapheresis</td>
<td>24</td>
<td>FSGS</td>
<td>complete</td>
<td>Relapse-Graft loss</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>plasmapheresis</td>
<td>13</td>
<td>ME</td>
<td>no</td>
<td>Graft loss</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>plasmapheresis</td>
<td>21</td>
<td>FSGS</td>
<td>complete</td>
<td>Relapse-Graft loss</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>plasmapheresis</td>
<td>25</td>
<td>FSGS</td>
<td>partial</td>
<td>Relapse-Graft loss</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>pefloxacin</td>
<td>25</td>
<td>FSGS</td>
<td>complete</td>
<td>Creatinine level 16 (\mu)mol/l</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>pefloxacin</td>
<td>MCD</td>
<td>no</td>
<td>Graft loss</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>No specific treatment</td>
<td></td>
<td>ME</td>
<td>no</td>
<td>Graft loss</td>
</tr>
</tbody>
</table>

MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; ME, mesangial expansion; IA, immunoadsorption.
(Figure 1) was significantly lower in the R group compared with the NR group (57% vs 82%, \( P < 0.001 \)). In the R group, 8 patients lost their graft and 4 maintained a functional graft until last observation. Causes of graft loss included recurrent NS in 7 cases and acute rejection in 1 case. One patient died with normal renal function. In the NR group, 4 patients lost their graft for chronic rejection and 3 patients died with a functional graft. Overall 5-year patient survival was 89.5%, respectively 91.7% in the R group and 82.6% in the NR group (\( P = 0.43 \)). Mean serum creatinine levels in patients with functional graft at the end of follow-up were respectively 139 μmol/l ± 35 in the R group and 151 μmol/l ± 31 in the NR group (\( P = \text{NS} \)).

**Discussion**

Among glomerulopathies, FSGS has the highest recurrence rate after renal transplantation. The recurrence rate recorded in the present study is 34% which is higher than the 25% overall estimated risk for recurrent glomerulopathy [5,19] but similar to the mean recurrence rate recorded in patients grafted with FSGS as primary disease [2,6,23].

The current study allows us to identify two significant factors associated with an increased risk for recurrence. The first factor concerns the use of cyclosporine as initial FSGS treatment. Our results suggest that recurrence occurs more frequently in patients with initial refractory or relapsing NS, the usual indication of cyclosporine therapy in FSGS [24]. The rapidity of evolution of the initial disease, a previously reported risk factor for recurrence [3,5,16–18] did not influence the recurrence rate in our study, suggesting that the use of cyclosporine during the initial course of FSGS is an independent risk factor for recurrence. This could be related to the higher efficacy of cyclosporine to prevent recurrence after transplantation in patients untreated with cyclosporine during the initial course of FSGS. In fact, almost all patients from the R and the NR groups received calcineurin inhibitors (CI) after transplantation. Thus, it might be hypothesized that the use of CI participates in the control of the recurrent process in some patients but is inefficient in others. Almost 57% of patients from the NR group did not receive cyclosporine during the primary course of FSGS. Perhaps, some of them would have been sensitive to cyclosporine therapy at this time, since they did not relapse after transplantation with an immunosuppressive regimen including CI. Conversely, it is likely that the 83.5% of patients from the recurrent group failed to respond to cyclosporine (or Tacrolimus) at the same time before and after transplantation. Another hypothesis to explain the higher recurrence rate in the group treated with CI during the initial course of FSGS, perhaps, some of them would have been sensitive to cyclosporine therapy at this time, since they did not relapse after transplantation with an immunosuppressive regimen including CI. Conversely, it is likely that the 83.5% of patients from the recurrent group failed to respond to cyclosporine (or Tacrolimus) at the same time before and after transplantation. Another hypothesis to explain the higher recurrence rate in the group treated with CI during the initial course of NS might be that patients with more severe forms of NS and with a higher risk of post-transplant recurrence received cyclosporine. The frequency of relapse has also been shown to be proportional to the mesangial proliferation on initial biopsy [16,18,20]. Our results support these previous findings although this association was not statistically significant between the two groups (41.6% vs 13% respectively in the R and the NR group).

In this study, the second significant risk factor associated with recurrence was donor age. [However, the difference was of borderline significance and because of the low number of patients, this result has to be interpreted with caution.] This has been previously reported by Choi et al. [25]. Elderly graft donors...
have a reduced number of functional nephrons and could be more sensitive to a circulating permeability factor. It has also been previously demonstrated that glomerular size was increased in patients after 30 years old and that glomerular size from patients with FSGS recurrence was also higher when compared with patients without recurrence [26]. This suggests that glomerular hypertrophy could play a critical role in the recurrence process as a permissive factor. Finally, donor age could act similarly to racial factors, accounting for the increased recurrence rate observed in white recipients grafted of African-American donor kidneys [27]. All these observations suggest that recurrence is more frequent when the donor nephron mass is not appropriate to the metabolic needs of recipients. However, it is clear that transplantation in children with a kidney from very young donors does not preclude recurrence in numerous cases, suggesting that donor age could only participate in the recurrence process, especially in recipients grafted with elderly donors.

In contrast to some reports [4,21,28], the immunosuppressive regimen did not influence the recurrence rate in our series. In particular, the use of ATG was not associated with a decrease in the recurrence. A higher recurrence rate in patients receiving induction therapy with ATG has been reported [21]. Since idiopathic NS is likely to be a T cell mediated nephropathy [29], the high recurrence rate in patients treated with T lymphocytes depleting therapy is a surprising finding, suggesting that other cell populations might participate in the recurrence process.

Delayed graft function has been reported to be more frequent in patients with recurrent disease [4,11]. In our study, the percentage of patients requiring dialysis after transplantation was higher in the R group compared with the NR group. Since relapse occurred very early (during the first 24 h) in 50% (6/12) of R group patients, the delayed graft function is likely to be related to the recurrence process. Recurrent FSGS has also been associated with an increased number of episodes of acute rejection in several reports [11,30]. Surprisingly, we report a higher number of acute rejections in the NR group compared with the R group. This could be related to the use of plasma exchange in the R group or, conversely, to an increase in the immunosuppressive regimen in patients with acute rejection. Nevertheless, we have previously shown that activated T cells of patients with idiopathic NS were early driven towards a Th2 phenotype [9,31]. Therefore, we cannot exclude that this ‘Th2 phenotype’ associated with recurrence precludes Th1 T cell activation associated with acute cellular rejection. These results suggest that there is no relationship between recurrence of NS and the risk of rejection.

Recurrence is likely to be mediated by a circulating factor but the structure and origin of this factor still remain unknown. The beneficial effect of immunoadsorption with protein A columns or plasma exchange observed in some patients might be related to the removal of this factor. Numerous studies reported the results of plasma exchange therapy in FSGS recurrence [2,15,26,30,32–34]. Most studies report a remission rate comprised between 70% and 80%, but 33% of patients relapse after the end of the treatment. In our study, plasma exchange therapy was used in 9 patients, leading to complete or partial remission in 8 cases. However, plasma exchange did not preclude graft loss secondary to recurrence in 6 patients (66%), highly suggesting that such a treatment rather induces transient remission than stable recovery, although successful use of plasmapheresis for long-term treatment has previously been reported [35,36]. Our results compare poorly with published data but plasma exchange is likely to be more effective (i) in paediatric patients than in adult recipients [37] and (ii) when given with other immunosuppressive therapy [30,38]. As previously reported [32,39], our results also suggest that early recurrence after transplantation and absence of mesangial proliferation on renal biopsy correlate with a better remission rate. In contrast, our study failed to establish correlations between either time to recurrence of proteinuria or time to initiation of plasmapheresis and response to plasmapheresis. Of interest, 2 recurrent patients were treated with success by pefloxacin without any other specific treatment. The effectiveness of this agent has not yet been established and data from literature are controversial [40–42]. However, it must be noted that negative results have currently not been reported after transplantation, suggesting that this drug could be helpful for a few patients. Nevertheless, since Pefloxacin can expose to tendonitis and tendon rupture, this drug should be used with caution. Here, we report for the first time 2 cases of recurrent FSGS successfully treated with Pefloxacin, suggesting that this treatment could represent an alternative therapeutic in these patients.

Finally, 50% of relapses led to graft failure and consequently, the overall 5-year graft survival was significantly lower in the R group compared with the NR group. These results are similar to previous reports [18,26,43,44] and confirm the benefit to identify in the future, clinical or biological predictive risk factors for recurrence. Despite the limited number of patients, our study also shows that donor age could be a reliable risk factor for recurrence in adult recipients. Moreover, our study suggests for the first time an opposite relationship between recurrence and acute rejection.

References


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