Recurrence of focal segmental glomerular sclerosis (FSGS) after renal transplantation

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Focal segmental glomerular sclerosis (FSGS) is a pathological term to indicate glomerular lesions associated with distinctive clinical features. In most cases, FSGS is primary in nature and is called idiopathic. Idiopathic FSGS is often associated with a nephrotic syndrome (NS) and may affect both children and adults. While the prognosis of FSGS is relatively good for patients with subnephrotic proteinuria, most patients with persisting proteinuria progress to end stage renal disease (ESRD) in spite of glucocorticoid or immunosuppressive treatment. For most of these patients, renal transplantation should be considered as the treatment of choice. However, in FSGS, the success of renal transplantation may be impaired by the frequent risk of recurrence of the disease on the allograft and by the poor graft survival rate in patients with recurrence.

This paper will focus on the risk factors for recurrence, the possible pathogenesis of recurrence and the clinical results of renal transplantation in patients with FSGS.

Risk factors for recurrence

In the first kidney allograft, ∼20 to 30% of patients develop recurrence of FSGS [1]. A number of factors have been reported to be associated with an increased risk of recurrence (Table 1). Second grafts, in those who have had recurrence in their first graft, are generally accompanied by a further recurrence [2]. Young children [3–5], patients with mesangial proliferation in the native kidneys [6], patients who received the kidney from an older donor [7], those who had a rapid progression to ESRD [4,6,8] and those who received pre-transplant bilateral nephrectomy [9] have been reported to have a higher risk of recurrence. Instead, neither the duration of dialysis [3,4] nor the type of post-transplant immunosuppression [3,10] influenced the risk of recurrence. Ethnicity and genetic background can also influence the risk of recurrence. A review of the United States Renal Data System (USRDS) found that the risk of recurrence was higher in white than in non-white patients [11]. Some investigators found that patients who have homozygous or complex heterozygous podocin mutations have a low recurrence rate [12,13]. However, Bertelli et al. reported that five of 13 children (38%) with inherited FSGS (nine with homozygous and four with heterozygous mutations of podocin) showed recurrence of proteinuria after renal transplantation, a rate of recurrence similar to that observed in FSGS children without mutations (12 of 27 or 44%), [14]. There are conflicting results with living donation. Baum et al. [15] reviewed the data of the North American Pediatric Renal Transplant Cooperative Study and found that the results of living transplants in children with FSGS were worse than in children without FSGS, the graft survival being similar to that observed in cadaveric renal transplant recipients without FSGS. Abbott et al. [11] reviewed the USRDS database and confirmed a higher risk of recurrence in living transplant recipients (18.7%) than in deceased donor transplant recipients (7.8%); however, after correction for other factors, living donor transplants had no association with graft loss from recurrent FSGS. Rather a living donor transplant was associated with superior overall graft survival. Cibrik et al. [16] also found that the risk of death-censored graft loss was 1% per year in patients who received a zero HLA mismatch kidney from living donors versus a 4.4% loss per year for patients who received a zero HLA mismatch kidney from cadaveric donors.

Clinical presentation

There are two clinical presentations of FSGS after transplantation: an early recurrence, the most frequent, characterized by a massive proteinuria within hours to days after implantation of the new kidney and a late recurrence which develops insidiously several months or years after transplantation.

In patients with early recurrence, proteinuria, usually in a nephrotic range, can precede the development of histological lesions that develop in a median 10–18 days after transplantation [17]. Early graft biopsies may show normal-appearing glomeruli by light microscopy but diffuse foot process effacement by electron microscopy. Segmental sclerosing lesions were associated with endocapillary proliferation, and foam cell accumulation may occur later and...
A role for co-stimulatory molecule B7-1 in podocytes as an inducible modifier of glomerular permeselectivity has been suggested. B7-1 in podocytes was found in genetic, drug-induced, immune-mediated and bacterial toxin-induced experimental kidney diseases with NS [26]. It is also possible that a subset of patients with FSGS may produce anti-actin, anti-ATP synthase, and anti-nephrin autoantibodies that may co-operate in altering glomerular permeability [27]. Recently, Charba et al. [28] have showed that the injection of antibodies directed against the protein tyrosine phosphatase receptor-O (a protein expressed on foot processes that regulates nephrin in the filtration barrier) increased the glomerular permeability to albumin. This report might suggest further mechanisms responsible for mechanisms leading to proteinuria and post-transplant recurrence of FSGS.

As T helper 2 and transcription factor c-Maf are activated during relapses of idiopathic nephrotic syndrome (INS), Bruneau et al. [29] investigated the possible role in recurrence of soluble ST2 (sST2) protein, a marker of T

Table 1. Factors influencing the risk of recurrence of FSGS

<table>
<thead>
<tr>
<th>Factors associated with increased risk of recurrence</th>
<th>Factors associated with low risk of recurrence</th>
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</thead>
<tbody>
<tr>
<td>Second transplant after loss from recurrence Childhood</td>
<td>Familial FSGS</td>
</tr>
<tr>
<td>Rapid progression to uraemia</td>
<td>Sporadic form with podocin mutation</td>
</tr>
<tr>
<td>Mesangial proliferation in native kidneys</td>
<td>Slow progression to uraemia</td>
</tr>
<tr>
<td>Living donation White race</td>
<td>Non-nephritic proteinuria in the original disease</td>
</tr>
<tr>
<td>Elderly donor</td>
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</tbody>
</table>

progress to glomerular sclerosis and interstitial fibrosis [18].

The occurrence of a late recurrence is rarer. The outcome of late recurrent FSGS is relentless but usually slower than in cases with early relapse. The differential diagnosis with segmental glomerulosclerosis caused by calcineurin-inhibitor (CNI) toxicity may be difficult. If renal biopsy is performed in the initial phases of recurrent FSGS, the electron microscopy shows the typical diffuse effacement of foot processes in case of classic FSGS. In case of glomerulosclerosis caused by CNI or other causes (obesity and hypertension), the foot process effacement is less noticeable and usually affects <50% of the glomerular capillary surface area. Frequently, the podocytes will show features of vacuolization, degeneration, hypertrophy and detachment for the underlying glomerular basement membrane. A typical arteriolaropathy, characterized by mucinoid thickening of the arteriolar wall or by nodular hyalinosis, may be seen in case of CNI toxicity. However, in the advanced phases, the differential diagnosis between recurrent FSGS and CNI toxicity is very difficult as both these complications cause segmental glomerular sclerosis associated with interstitial fibrosis and tubular atrophy.

Pathogenesis

The pathogenesis of recurrent FSGS is far from being established. Today, most investigators consider FSGS as a podocyte disease. The frequent occurrence of a rapid or even immediate relapse of proteinuria after transplantation led to postulate that podocyte injury could be caused by a circulating factor secreted by an abnormal clone of T cells [19]. Searching for this putative circulating factor, Savin et al. [20] found that the glomerular permeability to albumin was significantly increased in patients who had recurrence of FSGS after transplantation. After plasmapheresis in six patients with recurrence, the glomerular permeability and proteinuria significantly decreased. The authors hypothesized that the reason for the increased glomerular permeability could be a circulating factor bound to protein A with an apparent molecular mass of ~50 kDa. Dantal et al. [21] suggested that the albuminuric factor could be part of a complex with immunoglobulins. The possible pathogenetic role of a humoral factor was indirectly supported by the demonstration that the kidneys of a dead patient with FSGS transplanted into two uraemic recipients were free from proteinuria and that renal function was normal after 1 year [22]. More recently, Savin et al. [23] found that the permeability activity was carried by small, highly glycosylated, hydrophobic protein(s) or peptide(s). Other investigators, however, found that permeability factor activity was not specific for idiopathic FSGS as it was also present in other renal diseases [24]. Thus, despite intensive research, the nature of the circulating permeability factor remains unknown, and we still lack a reliable test for its presence and quantitation. The specificity and utility of bioassays in predicting recurrence have also given conflicting results. In one study, 11 of 13 children who tested positive for the permeability factor versus 4 of 12 with negative results had a recurrence of FSGS after renal transplantation [8]. Even in non-transplanted patients with idiopathic FSGS, no relationship has been found between the permeability activity and response to steroids, histological pattern at renal biopsy and long-term renal outcome [25].

More recently, the attention of the investigators has been focused on the inter-podocyte connections. The slit-diaphragm is structurally formed by extracellular proteins (such as nephrin, P-cadherin, etc.) anchored by a protein called podocin. It has been hypothesized that the permeability factor may induce redistribution and loss of nephrin as well as reduced expression of podocin. Cases of FSGS associated with mutation of the gene NPHS2, which encodes for podocin, have been reported both in familial and sporadic forms of FSGS. Until recently, the current opinion was that familial forms of FSGS do not recur, but the discovery that patients with sporadic FSGS and mutations of podocin may have a rate of post-transplant recurrence as high as that observed in patients with idiopathic FSGS [14] led to a re-evaluation of the problem. The risk of recurrence in patients with NPHS2 (podocin) mutation is low but not zero, around 8%. However, caution should be recommended in transplanting these patients with NPHS2 mutations with the kidney of their parents who are obligate carriers of NPHS2 mutation, because it could increase the risk of recurrence [13].
helper 2 cells and a factor predicted to be regulated by the transcription factor c-Maf. Actually, sST2 protein levels were significantly increased after transplantation in patients with INS recurrence compared with the two other groups. However, the sST2 protein was unable to induce podocyte injury in vitro or trigger proteinuria in rats, suggesting that sST2 protein is a marker of INS recurrence but is not involved in the development of recurrence. The same group of investigators [30] showed that the administration of the deoxyspergualin derivative LF15-0195 to Buff/Mna rats (which spontaneously develop FSGS with recurrence after transplantation) normalized proteinuria and led to the regression of renal lesions during both the initial disease and post-transplantation recurrence. Remission was also associated with a significant increase of splenic and peripheral CD4+CD25+FoxP3+ T lymphocytes. Of interest, the transfer of purified LF15-0195-induced CD4+CD25+ T cells to irradiated Buff/Mna rats significantly reduced their proteinuria compared with the transfer of untreated control cells, suggesting that LF15-0195 induces regulatory T cells that are able to induce regression of rat nephropathy. According to these data, INS/FSGS disease in rats can be regulated by cellular transfer, although it still remains to be elucidated whether and how this regulation leads to the reorganization of the podocyte cytoskeleton.

Clinical course and prognosis

Data about graft survival mainly come from large retrospective surveys with the biases typical of these kinds of analyses. The results may be different in children and in adults.

The graft survival is lower in children than in adults, particularly if the patient is white or Hispanic [4,11,31]. Compared to other renal diseases, the incidence of delayed graft function is higher and graft survival is lower in children with FSGS compared with other diagnoses [32]. Graft loss caused by recurrent FSGS is significantly higher in children receiving living donor transplants compared with cadaveric donor transplants in children [15,32]. A multivariate analysis of the data of the USRDS showed that besides the age and the ethnicity, acute rejection and cadaveric transplant were associated with worse results. In the same analysis, the 10-year graft survival rate was 70% for children receiving the kidney from a living donor [11].

The results are better in adults. A Cox proportional hazard model was used by Cibrik et al. [16] to estimate death-censored graft survival among FSGS patients. Those receiving a zero mismatch living kidney transplant lost 10.5 grafts per 1000 patients per year; not significantly different but higher, 14.3, was the graft loss rate for zero mismatch living kidney recipients with other glomerulonephritis. The graft loss rate was significantly higher, 36.5 per 1000 patients per year, in FSGS recipients who received a living mismatched transplant. Patients with FSGS who received a cadaveric zero mismatched graft or a cadaveric mismatched graft had significantly higher rates of graft losses (44.1 and 63.2 per 1000 patients per year, respectively) than those receiving a zero mismatched kidney from a living donor. Only few single-centre studies reported data on graft survival in adults with FSGS. Pardon et al. [33] reported a graft survival rate of 73% at 5 years in 33 transplanted adults with FSGS, with a significant difference between the patients with (57%) or without (82%) recurrence. No comparison with a control group was made. In 27 adults followed for a mean of 70 months, Choi et al. [7] reported a 10-year graft survival of 41% in patients who received a graft from donors younger than 40 years, while none of the grafts from donors older than 40 years was functioning at 10 years.

The renal prognosis is worse if one considers patients with a recurrence of FSGS on the allograft. A combined report in children on regular dialysis or renal transplantation pointed out that the median graft survival in children with recurrence of FSGS was only 5 months [34]. A report of the Renal Allograft Disease Registry showed that graft failure occurred within 32 months in 84% of adults with FSGS recurrence; the relative risk of graft failure was 2.25 when compared with patients without recurrence [35]. The risk of graft failure is particularly elevated in patients with early recurrence of FSGS [32]. Apart from the age and the time of recurrence, also renal histology can influence the outcome. The risk of recurrence is similar for the classic FSGS and the collapsing variant [36], but the development of collapsing FSGS after renal transplantation is associated with more severe vascular abnormalities, higher serum creatinine and a higher degree of graft failure than non-collapsing forms [36,37].

Treatment

The management of patients with recurrent FSGS and NS is difficult and not well established. Some investigators did not find any difference in the risk of recurrence and in the outcome of recurrent disease between patients treated with standard doses of cyclosporine (CsA) or with azathioprine [3,38]. Instead, an amelioration of proteinuria has been reported in a few children treated with very high doses of CsA [39]. The aim of such an approach was to compensate the lipid binding of CsA by elevated low density lipoprotein concentrations and the increase clearance of CsA seen in young children. After that report, some single-centre experiences confirmed the possibility of reversing proteinuria by giving oral or intravenous cyclosporine at high doses in children with recurrence of FSGS [17,40,41]. This anti-proteinuric effect of cyclosporine may be attributed both to suppression of T cells and inhibited production of their cytokines [42,43] and to the inhibition of calcineurin-mediated dephosphorylation of synaptopodin, a protein critical for stabilizing the actin cytoskeleton in kidney podocytes [44]. However, the long-term efficacy and tolerance of such a therapy remain to be established.

A good reduction of proteinuria in recurrent FSGS has been obtained in a number of patients by the pharmacological inhibition of the renin-angiotensin system with ACE-inhibitors, angiotensin-receptor blockers or the association of the two [45–47]. Sharma et al. [48] reported that synthetic analogues of 8,9-epoxyeicosatrienoic acids containing one double bond antagonized the effect of permeability factor, suggesting a therapeutic role for these agents in recurrent FSGS. The use of anti-tumour necrosis factor alpha agents...
The most commonly used therapeutic approach is represented by the use of plasmapheresis or immunoabsorption with protein A. A protective role of prophylactic plasmapheresis before transplantation has been reported [50,51]. However, plasma exchange and immunoabsorption have been mainly used for treating patients with an established recurrence. By reviewing the literature, we found that 49 of 70 (70%) children [8,52–61] and 49/77 (63%) adults [45,63–70] with recurrent FSGS who received plasmapheresis entered complete or partial remission of proteinuria (Table 2).

The best results were obtained when apheresis was started early after transplantation and repeated frequently. In one study, [70], a 14-day course of high-dose CsA and high-dose steroids associated with intensive plasmapheresis for up to 9 months allowed to obtain complete and sustained remission of proteinuria in nine of 10 patients with recurrent FSGS (mean proteinuria 0.19 g/day at 12 months). Another patient, who lost two previous grafts due to FSGS recurrence, became plasmapheresis-dependent and remained in partial remission at month 12. Taken together, these results are very encouraging showing a high rate of response both in children and adults. However, it is possible that these reports overestimated the benefit of plasmapheresis and immunoabsorption. The sample size was small, and the characteristics of patients were different, with the exception of two studies [45,66] with a historical control group, there was not a comparator group in the other reports. The definition of remission was different; the follow-up was usually short, and the long-term outcome, when available, was variable. While some patients maintained remission and good graft function, others who entered complete or partial remission had a relapse of nephrotic proteinuria within weeks or months, and a few other patients became plasmapheresis-dependent.

A long-term beneficial effect of rituximab, given weekly for 6 weeks, has been first reported in a child with a lymphoproliferative disorder and FSGS recurrence after transplantation by Pescevitz et al. [71]. Other single-case reports confirmed the benefit of rituximab either when given alone [72,73] or in combination with plasmapheresis [73–75], but failures were also reported [76,77]. In a multicentre retrospective review, seven children or young adults resistant to intensive plasmapheresis were treated with rituximab; three patients entered complete remission, two had a reduction of proteinuria of 70% and 50%, respectively [78]. However, in one series [79], no response at all was found after treatment with rituximab in four adults with recurrence of FSGS after kidney transplantation (Table 3). A case of reactivation of hepatitis B has been reported after treatment with rituximab in patients with recurrent FSGS [80].

Recently, Savin et al. [81] showed that the permeability factor has a high affinity for galactose. They tested the potential for galactose as a new therapy in a patient with post-transplant FSGS. The intravenous infusion of galactose decreased circulating permeability activity from 0.88 to undetectable levels up to 48 h post-infusion. However, it should be clear that there is no firmly established documentation for this treatment.

Conclusions and practical recommendations

In summary, recurrence of FSGS after transplantation is relatively frequent, particularly in children, in patients with rapid progression of the original disease, and in those who lost a previous transplant from recurrence. Preemptive plasmapheresis or immunoabsorption with column A may help in preventing recurrence of FSGS after transplantation.

### Table 2. Response (complete or partial) to plasmapheresis or immunoabsorption in children (first section) and adults (second section)

<table>
<thead>
<tr>
<th>Author</th>
<th>Children</th>
<th>Responders</th>
<th>Author</th>
<th>Adults</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
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<td>13</td>
<td>11</td>
<td>Dantal et al. [21]</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Laufer et al. [52]</td>
<td>2</td>
<td>2</td>
<td>Artero et al. [45]</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Kawaguchi et al. [53]</td>
<td>5</td>
<td>4</td>
<td>Matalon et al. [63]</td>
<td>13</td>
<td>4</td>
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<tr>
<td>Mowry et al. [54]</td>
<td>8</td>
<td>6</td>
<td>Moriconi et al. [64]</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cochat et al. [55]</td>
<td>3</td>
<td>3</td>
<td>Ponticelli et al. [65]</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cheong et al. [56]</td>
<td>6</td>
<td>2</td>
<td>Deegens et al. [66]</td>
<td>13</td>
<td>11</td>
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<tr>
<td>Saleem et al. [57]</td>
<td>3</td>
<td>1</td>
<td>Otsubo et al. [67]</td>
<td>11</td>
<td>3</td>
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<tr>
<td>Pradhan et al. [58]</td>
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<td>4</td>
<td>Valdivia et al. [68]</td>
<td>10</td>
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<tr>
<td>Haftner et al. [59]</td>
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<td>1</td>
<td>Singh et al. [69]</td>
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<td>0</td>
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<tr>
<td>Garcia et al. [60]</td>
<td>9</td>
<td>6</td>
<td>Canaud et al. [70]</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Fencel et al. [61]</td>
<td>2</td>
<td>1</td>
<td>TOTAL</td>
<td>77</td>
<td>49 (63%)</td>
</tr>
<tr>
<td>Mahesh et al. [62]</td>
<td>12</td>
<td>8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TOTAL</td>
<td>70</td>
<td>49 (70%)</td>
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</table>

### Table 3. Response (complete or partial) to rituximab

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
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<tr>
<td>Pescevitz et al. [71]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Apeland et al. [72]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Meyer et al. [73]</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Westphal et al. [74]</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Hristea et al. [75]</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Kamar et al. [76]</td>
<td>2 (2)</td>
<td>1</td>
</tr>
<tr>
<td>El-Firjani et al. [77]</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Strogolo et al. [78]</td>
<td>7 (7)</td>
<td>5</td>
</tr>
<tr>
<td>Yabu et al. [79]</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>19</td>
<td>11 (58%)</td>
</tr>
</tbody>
</table>

The numbers in the parentheses indicate the number of times the patients received plasmapheresis.
transplantation. Their use is advisable particularly in patients receiving the kidney from a living donor and in those who lost a previous transplant from recurrence.

After transplantation, proteinuria may herald the development of FSGS even if an early biopsy does not show glomerular abnormalities at light microscopy. Patients with post-transplant proteinuria >2 g/day who have FSGS as their original disease should be treated as soon as possible with an intensive course of plasmapheresis (an exchange a day for 3 days, then two to three exchanges per week for the first 2 weeks, followed by one to two exchanges per week, using 5% albumin as the replacement fluid). It should be kept in mind that in some cases, prolonged plasmapheresis, even for many months, is needed before seeing complete or partial remission of proteinuria. If a complete disappearance of proteinuria is obtained, plasmapheresis treatment may be stopped. A further course of plasmapheresis may be attempted in the case of relapse of nephritic proteinuria. If proteinuria improves but remains over 2–3 g per day, long-term plasma exchange therapy may be given at longer intervals. In one of our patients with recurrent NS, whenever plasmapheresis was interrupted, we continued plasmapheresis every 2–4 weeks for 7 years. The administration of high-dose ACE-inhibitors, angiotensin-receptor blockers and statins is also recommended in order to exploit their anti-proteinuric and anti-lipemic effects. Increased doses of steroids and calcineurin inhibitors may protect from FSGS recurrence but may increase the risk of over-immunosuppression. The role of rituximab should be better elucidated by further studies, but in the absence of contraindication, a course with rituximab may be attempted if there is no response to plasmapheresis. However, the optimal doses and duration of treatment with rituximab have not been established. In the few available reports, the schedules varied from 375 mg/m² every week for 4 weeks to 1 g given 2 weeks apart, repeated at 6 months. The potential of dexoxyspergualin or its derivatives is purely speculative at present.

In spite of the risk of recurrence, patients with FSGS should not be excluded from transplantation. In the case of living donation, the possibility of recurrence and its consequences should be clearly exposed to and discussed with the donor and the recipient and preemptive plasma exchange should be planned.

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References


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