Recurrent disease in renal transplants

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Abstract
Histology compatible with minimal change glomerulonephritis and associated with nephrotic syndrome has been reported as an occasional curiosity post-renal transplantation. Focal segmental glomerulosclerosis (FSGS) has a recurrence rate of ~20%. Age <15 years, an aggressive clinical course of the original disease and diffuse mesangial proliferation on native biopsy, are considered predictive of relapse. At present there are no tests that can accurately predict the likelihood of recurrence. Data from paediatric patients whose primary disease was FSGS were, on average, 90% more likely to lose a graft from a live donor and 50% more likely to lose a graft from a cadaveric donor compared with recipients with structural disorders. Recurrence in a subsequent graft is expected if the first graft was affected, but not if the first graft did not demonstrate recurrence. The best-established and most effective treatment of recurrent disease requires both plasma exchange and cyclophosphamide. Familial focal and segmental glomerulosclerosis, although rare, is important to recognize, as it is a different syndrome to idiopathic FSGS of childhood and overall transplant survival is good. Adults with ‘secondary’ FSGS would not be expected to be at risk of recurrent disease in a renal transplant.

Keywords: FSGS; recurrent disease; renal transplantation

Minimal change glomerulonephritis

Fourteen cases of renal transplant recipients developing nephrotic syndrome with minimal glomerular abnormalities have been reported although the cases do not represent true recurrence of a disease [1–7]. The prognosis is variable and follow-up often very short but in some reports there is progression to renal failure [4,7]. It is notable that re-biopsy in two patients showed focal segmental glomerulosclerosis (FSGS) [4]. Not all of the reports included venography or other imaging to exclude renal vein thrombosis and drug-associated effects are impossible to rule out.

Frequency of recurrence of focal segmental glomerulosclerosis and clinical progress

FSGS is an especially important problem in paediatric practice as it is responsible for ~10% of childhood idiopathic nephrotic syndrome [8,9]. The prognosis is poor with about one-third of patients progressing to end-stage renal failure within 5 years [10–14]. Recurrence of nephrotic syndrome after renal transplantation in patients with FSGS was first reported in 1972 [4]. Those individuals who do experience recurrent disease are also at high risk of delayed graft function. In one relatively large series of recipients who had FSGS as the primary diagnosis, delayed graft function occurred in 16 of 26 (61.5%) of grafts with recurrence compared with seven out of 47 (14.9%) of grafts without recurrence [15]. It was striking that in the same series recurrence in living donor transplants was associated with delayed graft function in four out of nine cases (44%) a proportion that is very much higher than would be expected in this group.

The recurrence rate varies with different series, but a large North American experience [16] reported 27 out of 132 patients (20.5%) and in Europe a rate of 20% in a series collected by the Paediatric European Dialysis and Transplant Association is documented [17], both papers having been published in 1992. More recent North American experience was reported in 1998 [18]. 1557 renal transplants performed at a single centre between 1984 and 1994 were reviewed and FSGS was discovered in 25 patients. Recurrent disease of all types, including other glomerulonephritides, diabetes and metabolic disorders, was established in only 6.3%
of patients. This emphasizes that recurrent disease in any particular renal transplant programme will be a rare diagnosis. As the study is retrospective and the indication for graft biopsy will vary, this figure represents a minimum estimate.

Some individuals will have proteinuria but adequate renal function for a number of years [19]. A retrospective analysis of a cohort of 29 paediatric patients who received 32 grafts between 1987 and 1998 in Northern Italy was published in 1999 [20]. In these individuals, proteinuria of >1 g/day occurred in 15 (52%) after the first transplant and in three out of three who received a second graft. The proteinuria almost always occurred early, in 14 out of 18 occasions in this report within the first month. In ∼70% of cases a transplant biopsy was performed. Recurrence of proteinuria was associated with a poor outcome compared with those individuals who did not experience recurrent disease. In the latter group ‘normal renal function’ after a mean follow up of 44 months was reported.

Recurrence of disease is not invariably associated with a dire prognosis. For five out of eight patients aged <25 years who lost primary renal transplants to recurrence FSGS, there was prolonged function of the graft of between 4 and 10.5 years [19]. Although one review article has recommended bilateral native nephrectomy as a prophylactic measure prior to transplantation [21], in the text the only reference is to a paper which points out that the manoeuvre will make the diagnosis of a recurrent FSGS post-transplantation easier [22]. The Advisory Committee of the 13th Renal Transplant Registry published in 1977 reported improved 4-year transplant survival with pre-transplant bilateral native nephrectomy and this was particularly true for patients with glomerulonephritis [23]. A more recent experience of 61 patients with bilateral native nephrectomy at risk of recurrent glomerulonephritis was compared with a group who had not undergone nephrectomy [24]. For FSGS the frequency of recurrence was significantly higher in those patients who had undergone nephrectomy, although the absolute number of affected individuals is small (Table 1). With a retrospective, non-randomized study it is of course possible that patients who proceeded to bilateral nephrectomy were a subgroup with more aggressive disease.

Familial focal and segmental glomerulosclerosis, although rare, is important to recognize, as it is a different syndrome to idiopathic FSGS of childhood. A recent large multinational survey identified 26 families with multigenerational involvement and 34 families with more than one individual in a single generation affected [25]. Patients presented on average in their third or fourth decade and, important in the context of recurrent disease post-transplantation, 41 individuals received a renal transplant and only one experienced recurrent disease; overall 10-year graft survival was 62%. A similarly good outcome after transplantation has been reported by others [26].

Adults with ‘secondary’ FSGS, for example due to renal artery stenosis or some other long standing conditions that lead to renal insufficiency, would not be expected to be at risk of recurrent disease in a renal transplant.

### Risk factors for recurrent FSGS

It is notable that certain factors, particularly age <15 years [27–32], aggressive clinical course of the original disease with time from diagnosis to end-stage renal failure of less than ∼3 years [12,27,28,31,33–37], and diffuse mesangial proliferation (DMP) on native biopsy [25,27,29,30,33,35,38,39], are considered predictive of relapse.

There is no ‘cut off’ that separates by age those patients destined to experience recurrence and those who will not [20]. Although in general age <15 years is considered to have a poor prognosis there is evidence that, within the paediatric group, those aged >6 years have a less poor prognosis. In a paediatric registry report in 1990, only 17% of children who were aged <6 years had relapse of nephrotic syndrome after transplantation compared with 40% of those aged >6 years at the time of diagnosis of the original glomerular disease [40].

In the Northern Italian experience [20] there was no difference in the gender distribution or age at onset of dialysis between the group with and without recurrent disease. However, the mean interval between diagnosis and end-stage renal failure was significantly shorter in the group with recurrence (Table 2). Disease duration from onset to dialysis was <2 years in nine of 15 patients with recurrent FSGS and two of 14 patients with non-recurrent FSGS (P < 0.014).

The importance of the native glomerular histology was explored in a publication that reported on 24 children who received 37 transplants. The native renal histology that was divided into three groups: pure FSGS, FSGS with focal mesangial proliferation (FMP) and FSGS with DMP [35]. As shown in Table 3, the finding of mesangial proliferation had a sinister prognosis for subsequent graft function.

### Table 1. Recurrence of FSGS in allograft

<table>
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<tr>
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<th>With nephrectomy n (%)</th>
<th>Without nephrectomy n (%)</th>
<th>P value</th>
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<tbody>
<tr>
<td>FSGS in native kidney</td>
<td>20 (93)</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>FSGS recurring in graft</td>
<td>8 (40)</td>
<td>15 (16.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Graft loss</td>
<td>5 (62.5)</td>
<td>8 (53.3)</td>
<td>&lt;0.02</td>
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</table>
De novo FSGS in renal transplants

This histological appearance has been most commonly reported associated with other pathology, usually 'chronic allograft nephropathy' [41–43] or transplant glomerulopathy [44,45] and occasionally cyclosporin toxicity [46] or IgA disease [47]. In a recent review of a database of 1706 transplant kidney biopsies, 293 patients had a biopsy diagnosis of chronic allograft nephropathy of which 87 (30%) also had de novo FSGS. This diagnosis was made relatively late, at a mean of 57 months post-transplantation, in contrast to recurrent FSGS. There were no differences between those with FSGS and chronic allograft nephropathy and those with chronic allograft nephropathy alone with respect to donor age, gender, race, cold ischaemia time or recipient characteristics such as age, gender, race, weight, presence of diabetes, panel reactive antibody peak or HLA mismatch [48]. In this series, only 24% of those with FSGS on biopsy had nephrotic syndrome and the mean 24-h protein excretion was 2.4 g. There was an important impact on graft survival with the diagnosis of FSGS; these patients had a 40% graft survival (death censored) at 5 years post-diagnosis, compared with 60% in those with chronic allograft nephropathy alone. Because of the association of FSGS and proteinuria, and the profound influence of the degree of the latter on graft survival, it was not possible using multivariate analysis to isolate statistically any other potentially important prognostic indicators.

Cadaveric or living related transplant donor source for patients with FSGS

Since 1987, the North American Paediatric Renal Transplant Co-operative Study has registered and followed all children who undergo renal transplantation in the USA and Canada. Patients with FSGS had, overall, the highest failure rates of patients with any primary diagnosis [49]. In this analysis, patients for whom the cause of end-stage renal failure was a 'structural problem', and presumably therefore correctable or irrelevant to renal transplant function, were assigned a relative risk of one. Patients whose primary disease was FSGS were on average 90% more likely to lose a graft from a live donor and 50% more likely to lose a graft from a cadaveric donor compared with the 'structural disorder' recipient. The 95% confidence interval for the patients with FSGS excludes unity and therefore is a statistically significant difference. Overall, however, recipients of a living donor kidney had a better graft survival (74.3%) compared with 58.9% for recipients of cadaveric renal transplants at 50 months. These authors commented that living donations 'are preferable for primary transplants in the majority of patients with FSGS'.

My practice would be to avoid living donor organ source as primary treatment if the clinical course of the original disease was < 3 years or if the patient was both aged < 15 years and had the histology of DMP. If the first transplant is lost to recurrent disease a living related transplant should be avoided for the subsequent grafting as the recurrence rate is 80% [12,19,31,35]. In contrast, if the first graft was lost from rejection or some other complication with no evidence of recurrence, it has been stated that there is little risk of recurrence in a subsequent graft [19]. It would follow that a live donor would be a good source in this situation. However, it should be appreciated that the advice is based on the experience of six cases, one of which lost the graft from rejection within 1 month of transplantation, so there is clearly not an absolute guarantee that recurrence will not occur.

Other anecdotes that argue for caution when utilizing living donors are three cases where FSGS and end-stage renal failure developed in donors who had donated a kidney to a sib with FSGS [50,51]. In all cases the donor had a normal work up with no urinary abnormalities prior to donation. The recently published UK Guidelines for Living Donor Kidney Transplantation recommends, as best practice, that living donor kidney transplantation should be avoided for children with FSGS and for adults with fulminant FSGS, but that
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re-transplantation from a living donor is reasonable if the first graft showed prolonged function or was free of FSGS.

Laboratory tests to predict recurrent FSGS

The recently reported observation that sera from patients with a recurrent FSGS causes an immediate profound increase in the albumin permeability of isolated rat glomeruli clearly offers the exciting possibility that at least the risk of recurrent disease for an individual patient could be more accurately predicted [52]. Subsequent experiments that have separated the sera obtained mostly during therapeutic apheresis into subfractions have demonstrated that the permeability factor is a protein of molecular weight between 30 and 50 kDa [53]. A Northern Italian group examined pre-transplant serum samples from 25 patients tested in an in vitro assay of glomerular permeability to albumin. FSGS recurred in 11 of 13 children who tested positive for the permeability factor and four of 12 patients with a negative test [20]. The odds ratio in the former group was 10.99 (with a 95% confidence interval of 1.6–75.5). However, using a different measure of glomerular permeability other authors have failed to find any predictive value of pre-transplant measurements on the risk of recurrence [54]. Given the relatively small number of affected individuals seen, a collaborative effort between several units will be necessary to confirm or refute these findings.

Treatment of recurrent FSGS post-transplantation

Plasma exchange and cyclophosphamide

Plasmapheresis is a technique that is relatively widely used for the treatment of recurrent nephrotic syndrome in this setting [20,37,55–62], usually in combination with other treatments, for example, cyclophosphamide, high-dose cyclosporin, angiotensin converting enzyme inhibitors [63] or indomethacin [64]. The Northern Italian group reported experience of treating 15 patients with recurrence in 18 grafts [20]. Because of the long interval necessary to collect the cases the base line immunosuppressive treatment was not uniform. Two patients received plasmapheresis and no alteration to other immunosuppressive treatment; stable remission was reported in one patient (followed for 52 months) and the other returned to dialysis after ~16 months. Eleven patients treated with plasmapheresis (removing 1–1.5 l each cycle depending on body weight with six to 10 treatments over 15–24 days) also received cyclophosphamide 2 mg/kg for 2 months. During these 2 months MMF or azathioprine was discontinued. In seven children remission was obtained with ‘normal renal function’ after a mean of 32 months of follow-up. The other four children lost grafts after an average of 15 months. These results are relatively good and similar to that seen by other authors [58] and I would interpret as encouraging the early institution of both plasma exchange and cyclophosphamide. A similar regimen but with longer cyclophosphamide treatment for 3 months and a longer duration of plasma exchange has recently been reported from Korea in six children recipients of living donor kidneys. The recurrences were all very early, within 3 days of transplantation. The results are far from encouraging with two patients in persistent remission at last follow-up, three with nephrotic range proteinuria and one graft had failed at 5 months [37].

Plasma protein absorption

Immunoadsorption with protein A columns followed by i.v. immunoglobulins has been used but only one patient out of eight treated showed a sustained response [65].

Angiotensin converting enzyme inhibitors

In nine patients with recurrent FSGS who received angiotensin converting enzyme inhibitors, only one of whom had plasma exchange as well, an impressive reduction in mean proteinuria from 11.1 to 4.22 g/day was seen [12]. There was no difference in mean allograft survival in those patients who received ACEIs (at a mean of 29.1 months) compared with those who did not (mean graft survival 26.2 months).

Cyclosporin

In an in vitro study, pre-incubation of rat glomeruli with cyclosporin A has been shown to attenuate greatly the increase in permeability when subsequently exposed to sera from patients with FSGS [66]. There is recent evidence, from a randomized trial of cyclosporin in patients with steroid resistant FSGS affecting native kidneys, of remission achieved with oral cyclosporin [67]. Some authors have reported control of proteinuria in paediatric transplant patients with presumed relapse of FSGS with high-dose cyclosporin [11,32]. The number of patients treated was small, for example two cases in one report [32], the dose of cyclosporin was very large (escalated from 15 to 27 to 35 mg/kg/day) and follow-up relatively short at 16 to 24 months. In an American report where cyclosporin use was delayed until after induction antibody therapy, the cyclosporin had no effect on proteinuria that was already present [65]. It has been pointed out that the frequency of relapse of FSGS has not altered when experience prior to the introduction of cyclosporin is compared with that seen after its widespread use [12]. One review has recommended i.v. cyclosporin early in the post-transplant course to maintain levels of 200–300 ng/ml, both as prophylaxis and for treatment [21]. However, as far as I know, the only published experience post-transplantation is limited to four children. All four showed complete remission soon after starting i.v. cyclosporin. Two children are free of proteinuria with
follow up of 9 and 15 months. One individual relapsed at 9 months and this relapse did not respond to another course of i.v. cyclosporin. The fourth patient lost the graft from rejection at 3.5 months [68]. This is far from compelling evidence for the use of this strategy.

**Tacrolimus**

Eleven patients were converted from cyclosporin to tacrolimus after the early recurrence of nephrotic syndrome. The first case was successful but the subsequent 10 patients showed no improvement and the authors concluded that rapid recurrent FSGS does not respond to treatment with tacrolimus [69]. A case report of a 30-year-old man with FSGS who developed nephrotic syndrome 5 years after renal transplant due to recurrent disease that occurred when he was switched from cyclosporin to tacrolimus suggests in adults that cyclosporin in this setting may be more protective than tacrolimus [70].

**Summary**

(i) Histology compatible with minimal change glomerulonephritis associated with nephrotic syndrome has been reported as an occasional curiosity after renal transplantation.

(ii) FSGS is an important problem with a high frequency of recurrent disease that is associated with premature graft loss.

(iii) Several clinical factors including age between 6 and 15 years, rapid clinical course of the original disease and the presence of mesangial proliferation predict a particularly high frequency of recurrence post transplantation.

(iv) Detection of a circulating factor may allow more accurate prediction of the risk of relapse in the future.

(v) Primary treatment with a live donor source is not recommended in the high-risk subgroup.

(vi) Recurrence in a subsequent graft is expected if the first graft was affected, but not if the first graft did not demonstrate recurrence.

(vii) The best-established and most effective treatment of recurrent disease requires both plasma exchange and cyclophosphamide.

(viii) Familial and secondary FSGS would not be expected to re-occur post transplantation.

**References**


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