

Focal Segmental Glomerulosclerosis (FSGS) Recurrence in Kidney Allograft Recipients

Oktawia Mazanowska and Dorota Kamińska

*Department of Nephrology and Transplantation Medicine Wrocław Medical University,
Poland*

1. Introduction

Primary or idiopathic focal and segmental glomerulosclerosis (FSGS) accounts for approximately 10% and 20% of cases of idiopathic nephrotic syndrome in children and adults, respectively. The primary pathophysiological process appears to be an injury of glomerular visceral epithelial cells, so-called podocytes, followed by an initial proliferation of mesangial, epithelial and endothelial cells with subsequent collapse of glomerular capillary loops and eventual sclerosis. The most popular pathogenetic hypothesis suggests the involvement of one or more circulating plasma factor(s), that appears to be protein between 30 and 50 kD molecular weight, altering glomerular permeability to proteins and causing proteinuria. Familial forms of FSGS occur due to mutations of several podocyte protein genes. FSGS can be a secondary process as well. Regardless of the etiology, the natural history of the disease include: peripheral edema, refractory proteinuria, hypertension, and progressive loss of renal function. FSGS frequently recurs after kidney transplantation with the recurrence rate of 30% after first transplantation, and 80% or more in the subsequent transplants. Risk factors of recurrence include a rapid progression of the primary disease to chronic kidney disease (CKD) stage 5, younger recipient age, early onset of nephrotic range proteinuria after kidney transplantation and frequent loss of the first and subsequent allografts. Considerable number of patients with recurrent FSGS respond to plasmapheresis (PP), especially if instituted early in the course of disease and before glomerulosclerosis has been established. Combined therapy with PP and cyclophosphamide may be beneficial. Other treatments consists of intravenous cyclosporine (CsA) and oral steroids. In some patients successful treatment of recurrent FSGS with the anti-CD20 monoclonal antibody, rituximab, in conjunction with PP has been reported. As a symptomatic treatment the use of ACE inhibitors should be recommended.

2. FSGS in native kidneys

Focal segmental glomerulosclerosis (FSGS) first described by Arnold Rich in 1959 (1) is a clinicopathological entity, characterized by focal and segmental occurrence of lesions with mesangial sclerosis, obliteration of glomerular capillaries with hyalinosis and intracapillary foam cells, formation of adhesions between the glomerular tuft and Bowman's capsule, and podocyte hypertrophy. Clinically FSGS is characterized by nephrotic syndrome (NS) and progressive loss of renal function. It is the most common histopathologic diagnosis

associated with idiopathic steroid-resistant NS in children, and one of the most frequent in adults, but in some patients, FSGS progress to CKD stage 5 without NS. Within 10 years of initial presentation, more than 50% of patients with FSGS develop CKD requiring renal replacement therapy (2). NAPRTCS 2007 Annual Report reveals that 14,3% of patients on dialysis and 11,4% of patients with renal transplant have FSGS as their primary diagnosis.

2.1 Pathogenesis of FSGS in native kidneys

The etiology of idiopathic FSGS and its post-transplant recurrence are still unclear; however, the recent studies on circulating permeability factor(s) (PF), genomics of podocin (NPHS2) and the emerging data on costimulatory molecules suggest an interplay of factors in different subgroups of patients with FSGS (3). Currently, FSGS is known to be due to an abnormality of the visceral epithelial cells (podocytes) of the glomerulus (4; 5). The morphological hallmark of primary FSGS is diffuse effacement of podocyte foot processes (usually > 80%), involving essentially all of the glomerular capillary loops. Damage of foot processes by the release of lymphokines/cytokines from T cells, possibly Th2 cells has been postulated (6). Transforming growth factor β (TGF β) is probably a mediator of scarring by induction of apoptosis of podocytes and adherence of the parietal epithelial cells to the naked GBM. The familial, genetic forms of FSGS result from abnormalities in gene transcription controlling assembly of slit diaphragm, actin-based cytoskeleton, and adhesion complexes, which are essential for the podocyte function in maintaining an effective filtration barrier. Some of the gene mutations in patients with FSGS include podocin (NPHS2), nephrin (NPHS1), α actinin-4 (ACTN-4), CD2-associated protein (CD2AP), WT1 transient receptor potential cation 6 (TRPC6), and phospholipase ϵ C (PLCE1/NPHS3) (7). FSGS can also be a secondary process due to underlying conditions including obesity, HIV or parvovirus B19 infection, plasma cell proliferative disease, lithium or pamindronate treatment, urinary reflux, and heroin abuse. The amount of foot processes effacement in secondary FSGS (usually < 30%) can be used as a morphological clue to distinguish primary and secondary process. A decreased ratio of podocytes to the glomerular filtration surface area appears to be the leading mechanism of secondary FSGS (8).

2.2 Role of permeability factor(s) or intrinsic podocyte defect

The pathogenesis of FSGS is not fully clarified, but injury of podocytes is crucial. Shalhoub was the first to propose the presence of a circulating mediator secreted by T cells (9), named permeability factor (PF) by Savin's group with an anionic charge and affinity for protein A and galactose and low molecular weight (10; 11). Though several studies strongly suggest the importance of the T cell origin circulating PF, this factor has not been completely identified biochemically and may not be specific for FSGS (7). A putative PF of molecular weight between 30 and 50 kDa has been isolated from sera of patients with FSGS and increased glomerular permeability to albumin (P_{alb}) *in vitro* (12). Permeability factor(s) may exert direct effects on the nephrin and podocin in the podocyte or may alter phosphorylation of cellular proteins in the podocyte, influence the activity of serine proteases or induce of integrin-like kinase activity that leads to detachment of podocyte from GBM (11;13; 14). This factor inhibits also the synthesis of nitric oxide, probably by up-regulating asymmetric dimethylarginine (ADMA) – an endogenous inhibitor of all nitric oxide synthases, with lose of anti-fibrotic effect in mesangium (15). Recently, McCarthy et al.

have identified a peptide - cardiotrophin-like cytokine 1 (CLC-1), which may be the presumed PF (16). Patients with a very high pretransplant level of PF had nearly 100% recurrence of their disease in the transplant kidney (12). Rarely PF may be present in patients with podocin (NPHS2) mutations. High pretransplant P_{alb} was found in 5 children with autosomal recessive podocin mutations, in which FSGS recurred after transplantation in four out of five (17). Since the PF is mildly anionic, it is unlikely that the effect of this factor is to neutralize the anionic sites on the GBM. Recent studies have suggested that there may be plasma factors that inhibit the PF (18; 19; 20). Furthermore, the net effect of the increased permeability may result from the absence or loss of an inhibitor for PF (19; 20). These inhibitory serum factors may be normal serum components such as apolipoproteins E and J (20). Further studies found that urine of patients with FSGS neutralize the PF activity of the serum, suggesting loss of an inhibitor in the urine (21), that may play a central role in the process after kidney transplantation and possibly also in the original disease (17). These findings suggest the deficiency of an inhibitor to the normally occurring PF as a primary cause for proteinuria. Alterations in the integrins ($\alpha3\beta1$) that are involved in the attachment of podocytes to the GBM might be important in some forms of FSGS (8). Novel pathway of injury in FSGS are probably CD80/86, transmembrane proteins normally expressed on the surface of B-cells and other antigen-presenting cells, that are important players of costimulation. Reiser et al. reported the novel role of CD80 in podocytes as an inducible modifier of glomerular permselectivity (22). The knockout mice lacking CD80 were protected from lipopolysaccharide (LPS)-induced NS (22). In experimental model, LPS up-regulated CD80 expression on podocytes, resulting in rapid podocyte effacement and severe proteinuria. This link between an innate immune response and gene mutations regulating a slit-diaphragm components may represent a novel scheme for understanding the pathogenesis of recurrent FSGS in some patients (22).

2.3 Role of gene mutations for proteins exclusively expressed by podocytes

Recent studies on gene mutations encoding podocin and other components of slit-diaphragm have underscored the heterogeneity of the idiopathic forms of FSGS. Alterations of the slit-diaphragm assembly can lead to changes in the selective barrier function, resulting in proteinuria. The discovery of gene mutations of the slit-diaphragm exclusive proteins in familial NS represented a breakthrough in the research of mechanisms of NS in humans. Mutations of NPHS2 gene (encoding for podocin and localized on chromosome 1q25-31), are the most common cause of familial NS and sporadic inherited FSGS. Homozygous carriers of NPHS2 mutations develop massive proteinuria in early childhood, not responding to common therapies and progressing to CKD stage 5 (23; 24; 25). So, in children seek for podocin mutations is justified to avoid a useless prolonged course of corticosteroids because of steroid resistance. As a corollary, proteinuria should not recur in patients with NPHS2 mutations because the molecular defect of podocin should be vanished. But the recurrence of the FSGS is observed also in these patients. The recurrence of proteinuria after renal transplantation in homozygous carriers of podocin mutations is associated with high values of permeability activity for albumin (P_{alb}); which suggest a role of PF also in this inherited condition. Heterozygous carriers of NPHS2 mutations (including variants) present variable clinical phenotypes with later onset of proteinuria. Tsukaguchi et al. found that the R229Q heterozygous variant of NPHS2 (which is found in FSGS patients with the same frequency as in a normal population) appeared not to cause FSGS, but rather to enhance susceptibility to

FSGS in association with a second mutant NPHS2 allele (26). In authors material two out of 10 patients with FSGS in native kidneys revealed R229Q heterozygous variant and only one of them experienced recurrence of FSGS during the first month after transplantation (27).

3. FSGS recurrence after kidney transplantation

Recurrent FSGS after renal transplantation was described by Hoyer et al. in 1972 (28). Nowadays FSGS is the most common kidney disease known to recur after kidney transplantation and only a small proportion being *de novo*. Recurrence rate of FSGS in pediatric patients is 50% and 30% in adults (29). A reliable estimate is approximately 30% to 40% at a first graft, with an exponential increment of risk (up to 80%) at subsequent renal grafts (30; 31; 32; 33). Patients with recurrent FSGS have higher incidence of delayed graft function (DGF) and five-year graft loss rates 30-50% and up to 80% over a follow-up period of 10 years (27; 31; 34; 35; 36; 37). The most popular hypothesis suggests the involvement of one or more circulating PF altering renal permeability to proteins and causing proteinuria in allograft. According to this possibility, removal of the putative PF by plasmapheresis (PF) or selective procedures with protein A column associated with a course of immunosuppression would restore a good long-term outcome of the graft. Patients with high pretransplant P_{alb} activity have a higher risk of FSGS recurrence (30). The impact of recipient age on FSGS recurrence was confirmed by Bertelli et al. in patients without mutation of podocin with early recurrence of proteinuria in 44% of younger patients and in 23% of the older ones (30). It is taken as a proof of the existence of circulating PF(s) that are also putative effectors of original proteinuria in these patients (30).

3.1 FSGS recurrence in patients with NPHS2 mutation

Patients with clearly two pathogenic NPHS2 mutations, although have early onset of NS in native kidneys, have a very low risk (about 3%) of FSGS recurrence after kidney transplantation compared with non-NPHS2 FSGS patients (recurrence rate about 34%) (25; 30; 38). On the other hand, simple heterozygous NPHS2 mutations have a similar high recurrence as the non-familial forms (29). Recurrence of proteinuria after kidney transplantation in patients with homozygous NPHS2 mutation is caused by other pathomechanism because the transplant kidney is free from podocin mutation and the one possibility is the development of autoantibodies against the unmutated protein of the transplanted kidney, however, no antipodocin antibodies were detected (38). The alternative explanation is the co-presence of circulating PF in affected patients. In these patients good effects of plasmapheresis and/or augmented immunosuppressive treatment might support the hypothesis that possibly both genetic and endogenous systemic factors play a role in recurring pathology. Heterozygous NPHS2 mutation carriers (affected with only one NPHS2 mutation) should be distinguished from patients with two pathogenic mutations of the NPHS2 gene (homozygous or compound heterozygous mutation carriers); only the latter condition fulfill the genetic criteria of autosomal recessive disease. The percentage of patients with only one NPHS2 mutation was low (2-3%) given the fact that a second mutation has not been missed (38). Some of the homozygous carriers of podocin mutations present early recurrence of proteinuria after renal transplantation in association with high values of P_{alb} , which suggest a role of PF also in this inherited condition (30). Carraro et al. revealed the high pre-transplant P_{alb} activity in 5 children with inherited FSGS due to autosomal recessive podocin mutations (17). The post-transplant outcome was complicated

in two (with 413G>A mutation) by recurrence of proteinuria after 10 and 300 days with high P_{alb} levels at onset that decreased to reach normal levels in the absence of proteinuria after the 7th cycle of PP. Co-incubation of serum with homologous nephrotic urine reduced P_{alb} to 0, whereas normal urine did not determine any change, which suggest loss of inhibitors in nephrotic urine. These data indicate that P_{alb} may be high also in NPHS2 mutated patients, probably resulting from loss of inhibitors in urine and lack of correlation of P_{alb} with proteinuria suggests a selective loss of inhibitors. In fact, high P_{alb} levels are strongly predictive of post-transplant recurrence of FSGS and P_{alb} is removed with *ex vivo* techniques such as PP and immunoabsorption. Loss of inhibitors may play a central role in the process, leading to recurrence in the allograft and possibly to proteinuria also in the original disease. (17).

3.2 Clinical manifestation and risk factors

Recurrent FSGS presents clinically with proteinuria or even full-blown nephrotic syndrome. Although recurrence of FSGS negatively influence kidney allograft survival, it has also been noticed that some individuals with proteinuria have adequate kidney function for years. Recurrence may be evident within days post-transplant (as early as the first 48 to 72 h), particularly in children (29; 38). Recurrence of FSGS can also develop any time within the first two years post-transplant. Multiple risk factors have been associated with recurrence of FSGS in the allograft. Children less than 15 years of age (generally between 6 and 15 yr), especially Caucasian white have a greater risk of recurrence (up to 40%) than do adults (36; 39). An aggressive course of primary FSGS prior to transplant, with a time interval between onset of the disease and CKD stage 5 less than 3 years is associated with higher recurrence rate (36). Both male gender and high pretransplantation panel-reactive antibodies (PRA) levels were noted to be independent risk factors for graft loss from recurrent disease. Also patients with mesangial hypercellularity in most of glomeruli as well as fewer sclerotic glomeruli have an increased incidence of recurrence (40; 41). Those with collapsing histology on native kidneys biopsy, tended to recur with the same histology and the presence of collapsing variant in the native kidney biopsy is a risk factor for recurrence (33; 42). Patients with history of prior transplant loss secondary to FSGS recurrence have a very high risk of recurrence in the current allograft, with rates as high as 80% in the second transplant and > 90% in the third and subsequent transplants (36; 43). Some studies have demonstrated higher rate of recurrence in recipients of living related grafts; probably due to closer HLA matching between living versus deceased donor or the phenotypic characteristics shared by related donor-recipient pairs that may render the kidney more susceptible to humoral factors. So some centers do not use living related allografts when transplanting particularly children (43). The more recent studies do not certify these findings, but with no advantage of graft survival in living donor transplants as observed in non-FSGS patients (44). In general living donation kidney transplantation should be avoided for children with FSGS and for adults with fulminant FSGS, but in patients not at high risk for recurrent FSGS or if the first graft showed prolonged function or was free of FSGS, living donor allografting could be considered, provided the fact that donor and recipient have been informed about the risk of disease recurrence associated with possible renal graft failure (38).

3.3 Laboratory and microscopic findings

There were no significant difference in serum creatinine concentration at the time of diagnosis between patients with and without FSGS (45). Proteinuria (at nephrotic range in many cases) and lipid levels were significantly greater in patients with FSGS (45).

Renal biopsy is often needed for definitive diagnosis, but early biopsies mostly show minimal changes on light microscopy. Effacement of foot processes on electron microscopy is the initial finding on renal biopsy, appearing within one week of recurrence. Light microscopy findings develop several weeks later (46). Hence, during the early post-transplant period, the diagnosis of FSGS recurrence, while suspected, is difficult to certify. Later, biopsies may show evidence of FSGS of the same histological subclass as in native kidneys (with 81% conformity) (47). ILPelaar et al. proposed three distinct patterns of recurrence: type I with fidelity to native disease (60%), type II with fidelity to native disease after a minimal change intermediate (20%), and type III with no fidelity to native disease (20%) (47). Arteriolar hyalinosis is more common in patients with FSGS than in patients without FSGS but the degree of interstitial fibrosis and tubular atrophy (IF/TA) was not significantly different (45).

4. Treatment of FSGS in kidney allograft recipients

Treatment strategies for recurrent FSGS are designed to inhibit secretion of the putative lymphocyte-derived PF by calcineurin inhibitors and enhance removal of PF by plasmapheresis (PP) or combined therapy with PP and cyclophosphamide. Recent reports have described the efficacy of anti-CD20 monoclonal antibody, rituximab, in conjunction with PP. Other treatments consists with intravenous cyclosporine (CsA) or high dose oral steroids. As a symptomatic treatment the use of ACE inhibitors may be recommended. But pharmacologic treatment options in recurrent FSGS are limited since most renal transplant recipients are already on maintenance steroids plus CsA or Tac, the medications most effective in the treatment of idiopathic FSGS as well (48). Because of the increased risk of graft loss in renal transplant recipients with FSGS, aggressive therapy should be recommended (37). The response of patients to PP seems to be completely individual. About 50% of patients with recurrent FSGS respond to PP, especially if instituted early in the course of disease and before glomerulosclerosis has been established. Individuals who develop recurrent FSGS after transplantation usually are given a trial of PP therapy (49). Some Centers have added oral Cyclophosphamide (2 mg/kg/day for 2 months) that reduces lymphocyte numbers and alters the balance of lymphocyte subsets or mycophenolate mofetil (MMF) to the PP protocol (40; 41). Therapeutical success in these studies have been variable. The other potentially benefit treatments is immunoadsorption with protein A columns followed by IVIG (38). Anti-proteinuric and anti-hypertensive effect of agents acting on renin-angiotensin system (ACEI and ARB) in patients with various nephropathies has been demonstrated also in recurrent FSGS (50), with 48-31% reduction of proteinuria, respectively, but with concern for graft dysfunction if early used post-transplant. Statins reduce the overall all-case as well as cardio-vascular mortality in post-transplant patients (51). The lipid-reducing treatment is significantly more common in patients with FSGS, and the level of proteinuria correlated significantly with cholesterol and TG levels. The use of lipid-lowering agents correlates with better graft prognosis; probably these drugs are used more commonly in older renal transplant recipients and with lower serum creatinine levels, and these two variables correlate with better graft survival or by pleiothropic effect of HMG-CoA reductase inhibitors on arteriolar endothelium (45). Hypercoagulable state is an important modifiable risk factor in NS also in recurrent FSGS. The work-up includes measuring of protein C, protein S, and anti-thrombin III levels and evaluating for presence of lupus anti-coagulant, anti-phospholipid and anti-cardiolipin

antibodies, and for factor V Leiden mutations in the blood. In the presence of evidence for thrombophilia, continuous intravenous heparin infusion with a goal to maintain an activated partial thromboplastin time (aPTT) of 1.5 times baseline is recommended for the immediate post-transplant period (52). Typically i.v. heparin can be switched to s.c. enoxaparin after 48 h post-transplant. Argatroban has been used if heparin is contraindicated because of the presence of heparin antibodies (52). Long-term anticoagulation is needed for at least one year post-transplantation and can be achieved with warfarin (53). Following transplantation patients with FSGS should be initially monitored daily, then weekly for proteinuria with either 24-h urine protein collections or with spot urine protein/creatinine ratio. The increase in spot urine protein/creatinine ratio should be confirmed by 24-h urine protein collection and followed by kidney biopsy.

4.1 Plasmapheresis and immunoadsorbent therapies

Plasmapheresis and Protein A immunoadsorbent therapy have been considered in the management of recurrent FSGS because recognizing the role of circulating PF in the pathogenesis. With the clinical and experimental evidence, PP as a therapeutic modality should be efficient but there are no controlled trials and reports are based on small series of patients. Plasmapheresis is most beneficial when used early in the course of recurrent FSGS when recurrence occurs early post-transplant (54). Pediatric patients seem to have better outcomes in response to PP, with remission rate of 60% to 80% (33; 48). The PP protocols vary with number of PP sessions and most patients need between 8 and 12 treatments to achieve remission. The good results occurred using a protocol of plasma exchange (1.5 plasma volumes) for 3 consecutive days followed by every other day for a total of 9 treatments using 5% albumin replacement. Other typical PP prescription is 1-2 times plasma volume exchanges (usually 60 ml for every 1 kg body weight per session) and about 3-4 treatments per week until remission is achieved, usually about 10 sessions. Schachter et al. found that PP resulted in complete or partial remission in 75% of those with recurrence (3/12 complete and 5/12 partial remission; partial remission was defined when proteinuria was decreased by 50%) and 25% of patients remained dependent on regular plasma exchange to prevent recurrence of proteinuria (55). Prophylactic PP with 8 single-volume treatments over 2 weeks prior to transplantation has been attempted in patients at high risk for recurrence with variable outcome, in case reports success varied from 50% (56) to less significant benefit. Living donor transplant candidates received the first treatment one week before transplantation, and deceased donor transplants received the first treatment within 24 hours of transplant. The preemptive PP, in the week before transplantation, led to significant reduction in the rate of recurrence. But in the study of Gonzales et al. the preemptive PP (1-10 sessions) did not decrease the rate of recurrence after transplantation but was beneficial in treating high-risk patients with documented recurrence, who can achieve good graft survival (57). Some centers have added cyclophosphamide and/or mycophenolate mofetil (MMF - 2 g/day in two divided doses) to the PP protocol, but with variable results (40; 41). In report by Fuentes et al. FSGS recurrence rate was 56.3% after the first and 80% in the second transplant in children (33). Plasmapheresis treatment was carried out in 7 of 9 patients, achieving remission in six of them. Recurrence of FSGS limited graft survival (first year 66% vs 85%, third year 20% vs 68%). The report shows that PP can be effective in treating FSGS recurrence in children, although its effect on long-term graft survival seems to be more limited (33). Matalon et al. in a group of 13 adult renal transplant recipients from 3 transplant centers who underwent PP for recurrent FSGS found 50% or

greater decline in proteinuria in 7 of 13 patients, but 3 of them (23%) remained PP-dependent (and required PP treatments every 2-4 weeks for up to 6 years to prevent progressive increase in proteinuria) (48). Five nonresponders progressed to CKD stage 5 over a mean time of 17 months from the recurrence. The only clinical parameter of prognostic significance was a short time interval between recurrence of FSGS and initiation of PP (48). Columns coated with staphylococcal protein A are used to treat FSGS because of the circulating factor affinity. In one study, patients were treated with protein A immunoadsorption columns with significant reduction of proteinuria and the decrease of proteinuria was about 82% at the end of the cycle (58).

4.2 Immunosuppression

Calcineurin inhibitors: The use of cyclosporine A (CsA) has not reduce the incidence of recurrent FSGS, but high doses ameliorate the clinical course of affected patients. There is consistent evidence that CsA diminishes or abolishes proteinuria. The exact mechanism of CsA in inducing remission is unknown, but immunosuppressive effects of CsA primarily result from inhibition of T helper cell activation and inhibition of release of cytokines/lymphokines, increase in glomerular cAMP as well as inhibition of glomerular PF or non-immunological effect with renal vasoconstriction. High-dose therapy with a goal to maintain high trough CsA blood level (recommended 125 to 200 ng/ml) suggest some beneficial effects (59). The reason of high whole blood CsA level is to overcome the effect of high serum cholesterol level in NS, because CsA is incorporated into the peripheral lymphocytes through LDL receptors on the cell surface. High blood level of LDL increase the amount of CsA bound to LDL and reduces the cellular uptake of LDL-CsA complex (60). In report of Salomon et al. in 14 out of 17 children treated with CsA (3mg/kg/day intravenously) for 3 weeks followed by an oral dosage to maintain trough levels between 200 and 300 ng/ml remission was achieved within 28 days (61). In other report the high-dose oral CsA (initially from 6 mg/kg/day in two divided doses) was necessary for inducing remission with complete and partial remission in 81% of treated patients (62). High dose CsA has also been used in connection with PP, but also the success was variable (38; 41; 62). Some experience in the treatment of FSGS has been reported with tacrolimus (initially at dose 0,15 - 0,1 mg/kg/day in two divided doses) and adjusted to the recommended trough blood level (5-10 ng/ml).

Rituximab: Rituximab is a chimeric mouse/human monoclonal antibody, acting on CD-20 surface marker of B-lymphocytes with selective depletion of B-lymphocytes. In transplantation rituximab is used to treat antibody-mediated rejection. Results of same very small cases series of rituximab in post-transplant recurrence of FSGS are inconsistent (63; 64). The typical regimen is 2-6 doses of 375 mg/m²/dose of rituximab given once every one to two weeks. The efficacy of rituximab in recurrent FSGS is limited. The report of Rodriguez-Ferrero et al. summarize the effect of rituximab associated with PP treatment of 3 adult renal transplant recipients with recurrent FSGS after a 4th, a second or a third renal transplantation, respectively (65). All the patients were treated with PP once a week after recurrence; the first and second patients were treated with PP also before transplantation (133 and 62 sessions) to prevent FSGS recurrence. All of the patients received rituximab (375 mg/m²/wk, 4 doses) and 1 PP session before each rituximab dose. The effectiveness of therapy was demonstrated by lack of peripheral CD19 cells after therapy. None of the patients treated with rituximab achieved complete remission, but in one patient proteinuria was reduced by 26%, in the second by 44% (65). Also Yabu et al. did not observed any

advantage of rituximab therapy. Authors report 4 adult patients (3 women, 1 man; three of them received kidney transplant from living-donor) with early recurrent FSGS refractory or dependent on PP who received rituximab as sole therapy (total dose 2000 – 4200 mg). None of the patients treated with rituximab achieved remission in proteinuria, and one patient experienced early graft loss (66).

Corticosteroids: There are no data or controlled trials on corticosteroid (CS) as a sole treatment in recurrent FSGS, because patients are treated with CS in combination with CsA and/or PP. The caution is necessary when diminishing CS dosage after kidney transplantation in patients with FSGS in native kidneys (67).

In summary, even though there are no well-conducted studies, aggressive therapy of recurrent FSGS using plasmapheresis is considered to be a treatment of choice for this condition, with or without high-dose CsA, cyclophosphamide and/or MMF. However, the response is completely individual and many patients do not show improvement with any of these therapies (49).

5. Prognosis

Patients with FSGS often undergo renal transplantation because they are younger and have little comorbidity, and they are considered good transplant candidates (68). Unfortunately, recurrence of FSGS in the allograft is common. Once the FSGS has recurred in the allograft, loss of the graft occurs within 1 year in 50% to 80% of patients who do not receive any extra or specific treatment (41). FSGS patients who receive renal transplants have a 2-fold higher risk of losing graft at 10 years, compared to all patients transplanted for glomerulonephritis (37; 69). In report of Fuentes et al. in pediatric patients with recurrent FSGS graft survival was lower than in those with other etiologies of CKD (first year 75% vs 91%; 5th year 44% vs 78%) (33). In Schachter's material recurrence rate was 23% of patients with biopsy proven primary FSGS (55). Sener et al. have reported that post-transplant recurrence of FSGS may be associated with bilateral nephrectomy indicated in some patients with catastrophic NS (70). These patients should be monitored closely for early recurrence and may benefit from early PP treatment (70). The type of induction therapy for post-transplant immunosuppression is suggestive to have an effect on recurrence of FSGS as well, with higher incidence with the use of anti-lymphocyte sera (ALS) or anti-thymocyte globulin (ATG) in patients with primary FSGS. The use of ALS or ATG for initial induction therapy should be avoided in these patients because of increased recurrence rate of FSGS due to induction of certain T-cell subtypes and subsequent lymphokine/cytokine release and altering the slit-diaphragm (38). Although CsA seems to have no effect on the frequency of FSGS recurrence, there is evidence that CsA reduces proteinuria and prolongs graft survival in patients with recurrence after transplantation. Sirolimus should be used with care because of the increased possibility of recurrence (59). Although FSGS previously was associated with African-American race white recipients were at greater risk of graft loss resulting from recurrent disease. The mechanism of this association is unknown and should be investigated further (37).

The outcome of recurrent FSGS in a transplant kidney is variable, dependent on multiple factors and varies from immediate graft loss to slowly progressive proteinuria with chronic allograft injury to complete remission with no long-term consequences on the graft. Incidence of graft loss in the first 5 years post-transplant, in patients with recurrent FSGS varies, and is 20% to 50% (29). The data about the follow-up and outcome are inconsistent,

not only in the graft survival rates, but also in risk factors of graft failure. In the report of Cosio et al. a significantly greater number of patients with FSGS lost their graft (39%) compared with 26% of patients with chronic allograft injury but without FSGS (45). Moroni et al. described the quite good outcomes of 52 renal transplants in 47 adults with FSGS (68). FSGS recurred in 12 out of 52 grafts (23%) and led to graft failure in 7 within 10 months. In the other 5 cases, proteinuria remitted and grafts were functioning 106 months after transplantation. The second recurrence developed in 62,5% of re-transplanted patients, who lost their first graft because of recurrence, and only one graft was lost. Patients with recurrence were more frequently male subjects (83% vs 40%), younger at diagnosis of FSGS (16 yr vs 24 yr) and of younger age at transplantation (28 yr vs 36 yr). Graft loss resulting from a second recurrence was lower than expected, and treatment with PP (in nonresponsive patients), steroids, CsA plus ACE inhibitors achieved either complete or partial remission in 80% of the cases (68).

6. *De novo* FSGS after kidney transplantation

De novo FSGS occurs in patients without the diagnosis of FSGS in native kidneys and develops more than 6 months posttransplant (45). The pathogenesis for *de novo* FSGS in allografts is unknown but two potential pathogenic mechanisms seem particularly attractive: CsA toxicity and hyperfiltration, triggered by hemodynamic stress in remnant nephrons following injury to the allograft by rejection or ischemia. In fact, *de novo* FSGS has been reported with sirolimus use (71). Primarily the glomeruli in the outer cortical region are involved with occlusive vascular changes and sometimes collapsing glomerulonephritis. The histological picture differ from recurrent FSGS, where the mild obliterative arteriopathy preferentially involves the juxtamedullary glomeruli. Clinically, *de novo* FSGS presents with proteinuria and a less aggressive course than recurrent FSGS, but is also a negative independent predictor of graft survival. *De novo* FSGS in renal allografts most often is diagnosed in association with chronic allograft nephropathy or recurrent IgA nephropathy, transplant glomerulopathy, *de novo* membranous nephropathy but also may be not associated with other pathological conditions (45).

7. As summary

Due to increase incidence of FSGS and increasing numbers of FSGS patients coming to transplantation, the role of recurrent disease is becoming an area of greater concern to nephrologists and transplant physicians. The incidence of recurrence is generally accepted to be between 20% to 30%. Risk factors for and characteristics of recurrence include a rapid progression of the primary disease to CKD stage 5, early onset of nephrotic range proteinuria after allografting, frequent loss of the allograft, a high frequency of recurrence in subsequent allografts, and children less than 15 years of age. Some investigators have identified a circulating permeability factor, called the FSGS factor, that appears to be protein between 30 and 50 kD molecular weight. Logically, the association of PF with recurrence of FSGS guided to treat patients with plasmapheresis. The response of patients to PP seems to be completely individual. Modern immunosuppression regimens including tacrolimus, mycophenolate mofetil, sirolimus do not appear to provide additional benefit over older regimens with CsA and corticosteroids in preventing recurrence of FSGS. Patients with recurrence of FSGS clearly present a worse outcome than those who do not experience recurrent disease.

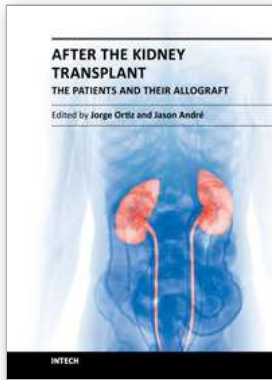
8. References

- [1] Rich AR.: A hitherto undescribed vulnerability of the juxtamedullary glomeruli in lipoid nephrosis. *Bulletin of the Johns Hopkins Hospital* 1959; 100: 173-186
- [2] Kitiyakara C., Edgers P., Kopp JB et al.: Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. *Am J Kidney Dis* 2004; 44: 815-825
- [3] Ghiggeri GM., Carraro M., Vincenti F.: Recurrent focal glomerulosclerosis in the era of genetics of podocyte proteins: theory and therapy. *Nephrol Dial Transplant* 2004; 19: 1036-1040
- [4] Kretzler M.: Role of podocytes in focal sclerosis: defining the point of no return. *J Am Soc Nephrol* 2005; 16: 2830-2832
- [5] Brenchley PE.: Vascular permeability factors in steroid-sensitive nephritic syndrome and focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2003; 18 (Suppl 6): vi21-25
- [6] Van den Berg JG., Weening JJ.: Role of the immune system in the pathogenesis of idiopathic nephritic syndrome. *Clin Sci* 2004; 107: 125-136
- [7] Woroniecki RP, Kopp JB.: Genetics of focal segmental glomerulosclerosis. *Pediatr Nephrol* 2007; 22: 638-644
- [8] Chen CA., Hwang JC., Guh JY., et al.: Reduced podocyte expression of alpha3beta1 integrins and podocyte depletion in patients with primary focal segmental glomerulosclerosis and chronic PAN treated rats. *J Lab Clin Med* 2006; 147: 74-82
- [9] Shalhoub RJ.: Pathogenesis of lipoid nephrosis: a disorder of T-cell function. *Lancet* 1974; 2: 556-560
- [10] Savin VJ., McCarthy ET., Sharma R., et al.: Galactose binds to focal segmental glomerulosclerosis permeability factor and inhibits its activity. *Transpl Res* 2008; 151: 288-292;
- [11] Sharma M., Sharma R., McCarthy ET., et al.: The focal segmental glomerulosclerosis permeability factor: biochemical characteristics and biological effects. *Exp Biol Med* 2004; 229: 85 -98
- [12] Savin VJ., Sharma R., Sharma M., et al.: Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. *N Engl J Med* 1996; 334: 878-838
- [13] Hattori M., Akioka Y., Chikamoto H., et al.: Increase of integrin-linked kinase activity in cultured podocytes upon stimulation with plasma from patients with recurrent FSGS. *Am J Transplant* 2008; 8: 1550-1556;
- [14] Carraro M., Zennaro C., Artero M., et al.: The effect of proteinase inhibitors on glomerular permeability induced in vitro by serum from patients with idiopathic focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2004; 19: 1969-1975
- [15] Trachtman H., Futterweit S., Singhal PC., et al.: Circulating factor in patients with recurrent focal segmental glomerulosclerosis postrenal transplantation inhibits expression of inducible nitric oxide synthase and nitric oxide production by cultured rat mesangial cells. *J Invest Med* 1999; 47: 114-120
- [16] McCarthy ET., Sharma M., Savin VJ.: Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2010; 5: 2115-2121
- [17] Carraro M., Caridi G., Bruschi M., et al.: Serum glomerular permeability activity in patients with podocin mutations (NPHS2) and steroid-resistant nephrotic syndrome. *J Am Soc Nephrol* 2002; 13: 1946-1952

- [18] McCarthy ET, Sharma M., Sharma R., et al.: Sera from patients with collapsing focal segmental glomerulosclerosis increase albumin permeability of isolated glomeruli. *J Lab Clin Med* 2004; 143: 225-229
- [19] Sharma R., Sharma M., McCarthy ET., et al.: Components of normal serum block the focal segmental glomerulosclerosis factor activity in vitro. *Kidney Int* 2000; 58: 1973-1979
- [20] Candiano G., Musante L., Carraro M., et al.: Apolipoproteins prevent glomerular albumin permeability induced in vitro by serum from patients with focal segmental glomerulosclerosis. *J Am Soc Nephrol* 2001; 12: 143-15024
- [21] Carraro M., Zennaro C., Candiano G., et al. : Nephrotic urine prevents increased rat glomerular albumin permeability induced by serum from the same patient with idiopathic nephritic syndrome. *Nephrol Dial Transplant* 2003; 18: 689-693
- [22] Reiser J., von Gersdorff G., Loos M., et al. : Induction of B7-1 in podocytes is associated with nephrotic syndrome. *J Clin Invest* 2004; 113: 1390-1397
- [23] Caridi G., Perfumo F., Ghiggeri GM.: NPHS2 (podocin) mutations in nephrotic syndrome. Clinical spectrum and fine mechanisms. *Pediatr Res* 2005; 57: 54R-61R
- [24] Boute N, Gribouval D., Roselli S., et al.: NPHS2 gene, encoding the glomerular protein podocin is mutated in autosomal recessive steroid-resistant nephritic syndrome. *Nat Genet* 2000; 24: 349-352
- [25] Weber S., Gribouval O., Esquivel EL., et al.: NPHS2 mutation analysis shows genetic heterogeneity of steroid-resistant nephritic syndrome and low post-transplant recurrence. *Kidney Int* 2004; 66: 571-579
- [26] Tsukaguchi H., Sudhakar A., Le TC., et al.: NPHS2 mutations in late-onset focal segmental glomerulosclerosis: R229Q is a common disease allele. *J Clin Invest* 2002; 110: 1659-1666
- [27] Mazanowska O., Kamińska D., Kościelska-Kasprzak K., et al: High risk of FSGS recurrence in kidney allograft recipients independent of heterozygous NPHS2 mutation. *Adv Clin Exp Med* 2008; 17: 207-212
- [28] Hoyer JR., Vernier RL., Najarian JS., et al: Recurrence of idiopathic nephritic syndrome after renal transplantation. *Lancet* 1972; 2: 343-348
- [29] Vinai M., Weber P., Seikaly MG.: Recurrence of focal segmental glomerulosclerosis in renal allograft: An in-depth review. *Pediatr Transplant* 2010; 14: 314-325
- [30] Bertelli R., Ginevri F., Caridi G., et al.: Recurrence of segmental glomerulosclerosis after renal transplantation in patients with mutations of podocin. *Am J Kidney Dis* 2003; 41: 1314-1321
- [31] Newstead CG.: Recurrent disease in renal transplants. *Nephrol Dial Transplant* 2003; 18 (Suppl 6): vi68-vi74
- [32] Couser W.: Recurrent glomerulonephritis in the renal allograft: an update of selected areas. A one-center study of plasma exchange effects. *Exp Clin Transplant* 2005; 3: 283-288
- [33] Fuentes GM., Mesaguer CG, Carrion AP., et al.: Long-term outcome of focal segmental glomerulosclerosis after pediatric renal transplantation. *Pediatr Nephrol* 2010; 25: 529-534
- [34] Baum MA: Outcomes after renal transplantation for FSGS in children. *Pediatr Transplant* 2004; 8: 329-333
- [35] Hickson LJ, Gera M., Amer H ., et al.: Kidney transplantation for primary focal segmental glomerulosclerosis: Outcomes and response to therapy for recurrence. *Transplantation* 2009; 87: 1232-1239

- [36] Tejani A., Stablein DH.: Recurrence of focal segmental glomerulosclerosis posttransplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study. *J Am Soc Nephrol* 1992; 2: (Suppl 12): S256-S263
- [37] Abbott K.C., Sawyers E.S., Oliver J.D.III, et al.: Graft loss due to recurrent focal segmental glomerulosclerosis in renal transplant recipients in the United States. *Am J Kid Dis* 2001; 37: : 366-373
- [38] Weber S., Tönshoff B.: Recurrence of focal-segmental glomerulosclerosis in children after renal transplantation: clinical and genetic aspects. *Transplantation* 2005; 80: S128-S134
- [39] Senguttuvan P., Cameron JS., Hartley RB., et al.: Recurrence of focal segmental glomerulosclerosis in transplant kidneys: analysis of incidence and risk factors in 59 allografts. *Pediatr Nephrol* 1990; 4: 21-28
- [40] Cheong HI., Han HW., Park HW., et al.: Early recurrent nephrotic syndrome after renal transplantation in children with focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2000; 15: 78-81;
- [41] Nathanson S., Cochat P., Andre JL., et al.: Recurrence of nephrotic syndrome after renal transplantation: influence of increased immunosuppression. *Pediatr Nephrol* 2005; 20: 1801-1804
- [42] Thomas DB, Franceschini N., Hogan SL., et al.: Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int* 2006; 69: 920-926
- [43] First MR.: Living-related donor transplants should be performed with caution in patients with focal segmental glomerulosclerosis. *Pediatr Nephrol* 1995; 9 (Suppl): S40-S42
- [44] Baum MA., Stablein DM., Panzarino VM., et al.: Loss of living donor renal allograft survival advantage in children with focal segmental glomerulosclerosis. *Kidney Int* 2001 59: 328-333
- [45] Cosio F.G., Frankel W.L., Pelletier R.P., et al.: Focal segmental glomerulosclerosis in renal allografts with chronic nephropathy: implications for graft survival. *Am J Kidney Dis* 1999; 34: 731-738
- [46] Requião-Moura LR., Moscoso-Solorzano GT, Franco MF., et al.: Prognostic factors associated with poor graft outcomes in renal recipients with post-transplant glomerulonephritis. *Clin Transplant* 2007; 21: 363-370
- [47] Ijpelaar D., Farris AB., Goemaere N., et al.: Fidelity and evolution of recurrent FSGS in renal allografts. *J Am Soc Nephrol* 2008; 19: 2219-2224
- [48] Matalon A., Markowitz G.S., Joseph R.E., et al.: Plasmapheresis treatment of recurrent FSGS in adult renal transplant recipients. *Clin Nephrol* 2001; 56: 271-278
- [49] Crosson J.T.: Focal segmental glomerulosclerosis and renal transplantation. *Transplant Proc* 2007; 39: 737-743.
- [50] White CT., Macpherson CF., Hurley RM., Matsell DG.: Antiproteinuric effects of enalapril and losartan: A pilot study. *Pediatr Nephrol* 2003; 18: 1038-1043
- [51] Navaneethan SD., Pansini F., Perkovic V., et al.: HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2009; (2): CD007784
- [52] Morrissey PE., Ramirez PJ., Gohh RY., et al.: Management of thrombophilia in renal transplant patients. *Am J Transplant* 2002; 2: 872-876
- [53] Kusyk T., Verran D., Stewart G., et al.: Increased risk of hemorrhagic complications in renal allograft recipients receiving systemic heparin early posttransplantation. *Transplant Proc* 2005; 37: 1026-1028

- [54] Pradhan M., Petro J., Palmer J., et al.: Early use of plasmapheresis for recurrent post-transplant FSGS. *Pediatr Nephrol* 2003; 18: 934-938
- [55] Schachter M.E., Monahan M., Radhakrishnan J., et al.: Recurrent focal segmental glomerulosclerosis in the renal allograft: single center experience in the era of modern immunosuppression. *Clin Nephrol* 2010; 3: 173-181
- [56] Gohh RY., Yango AF, Morrissey PE., et al.: Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. *Am J Transplant* 2005; 5: 2907-2912
- [57] Gonzales E., Ettenger R., Rianthavorn P., et al.: Preemptive plasmapheresis and recurrence of focal segmental glomerulosclerosis in pediatric renal transplantation. *Pediatr Transplant* 2011; doi: 10.1111/j. 1399-3046.2011.01478.x. [Epub ahead of print]
- [58] Dantal J., Bigot E., Bogers W., et al.: Effect of plasma adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. *N Engl J Med* 1994; 330: 7-14
- [59] Skhiri H., Morelon N., Noël LH., et al.: Unusual post-transplantation recurrence of focal segmental glomerulosclerosis which resolved with cyclosporine but not with sirolimus. *Transplant Int* 2005; 18: 458-460
- [60] Hirano T., Akashi T., Oka K., et al.: Serum cholesterol levels and kidney transplantation outcome: attenuation of cyclosporine efficacy? *Transplantation* 2001; 71: 659-660
- [61] Salomon R., Gagnadoux MF., Niaudet P.: Intravenous cyclosporine therapy in recurrent nephrotic syndrome after renal transplantation in children. *Transplantation* 2003; 75: 810-814
- [62] Raafat RH., Kalia A., Travis LB., Divens C.: High dose oral cyclosporin therapy for recurrent focal segmental glomerulosclerosis in children. *Am J Kidney Dis* 2004; 44: 50-56.
- [63] Apeland T., Hartmann A. : Rituximab therapy in early recurrent focal segmental sclerosis after renal transplantation. *Nephrol Dial Transplant* 2008; 23: 2091-2094
- [64] Hristea D., Hadaya K., Marangon N., et al. : Successful treatment of recurrent focal segmental glomerulosclerosis after kidney transplantation by plasmapheresis and rituximab. *Transplant Int* 2007; 20: 102-105
- [65] Rodriguez-Ferrero M., Ampuero J., Anaya F.: Rituximab and chronic plasmapheresis therapy of nephrotic syndrome in renal transplantation patients with recurrent focal segmental glomerulosclerosis. *Transplant Proc* 2009; 41: 2406-2408
- [66] Yabu JM., Ho B., Scandling JD., Vincenti F.: Rituximab failed to improve nephrotic syndrome in renal transplant patients with recurrent focal segmental glomerulosclerosis. *Am J Transplant* 2008; 8: 222-227.
- [67] Greenbaum LA., Hanevold CD.: Nephrotic syndrome after conversion to alternate day steroids in two children with a history of recurrent FSGS. *Pediatr Transplant* 2003; 7: 395-399
- [68] Moroni G., Gallelli B., Quaglini S., et al.: Long-term outcome of renal transplantation in adults with focal segmental glomerulosclerosis. *Transplant Int* 2009; 23: 208-216
- [69] Briganti E.M., Russ GR., McNeil J.J., et al.: Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med* 2002; 347: 103-109
- [70] Sener A., Bella AJ., Nguan C., et al.: Focal segmental glomerular sclerosis in renal transplant recipients: predicting early disease recurrence may prolong allograft function. *Clin Transplant* 2009; 23: 96-100
- [71] Letavernier E., Bruneval P., Mandet C., et al.: High sirolimus levels may induce focal segmental glomerulosclerosis *de novo*. *Clinical J Am Soc Nephrol* 2007; 2: 326-333



After the Kidney Transplant - The Patients and Their Allograft

Edited by Prof. Jorge Ortiz

ISBN 978-953-307-807-6

Hard cover, 386 pages

Publisher InTech

Published online 17, August, 2011

Published in print edition August, 2011

There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient's tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Oktawia Mazanowska and Dorota Kamińska (2011). Focal Segmental Glomerulosclerosis (FSGS) Recurrence in Kidney Allograft Recipients, *After the Kidney Transplant - The Patients and Their Allograft*, Prof. Jorge Ortiz (Ed.), ISBN: 978-953-307-807-6, InTech, Available from: <http://www.intechopen.com/books/after-the-kidney-transplant-the-patients-and-their-allograft/focal-segmental-glomerulosclerosis-fsgs-recurrence-in-kidney-allograft-recipients>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](#), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.