Abstract

Focal segmental glomerulosclerosis (FSGS) is a clinicopathological entity of not fully explained etiology characterized by focal and segmental occurrence of lesions. It is currently believed that primary FSGS is caused by alterations in glomerular epithelial cells (podocytes). FSGS is one of the most frequent causes of nephrotic syndrome in adults. The course of the disease is strongly influenced by proteinuria or nephrotic syndrome and renal insufficiency at presentation. The prognosis of FSGS is poor because there are no spontaneous remissions and because of resistance to treatment. FSGS has a high recurrence rate after kidney transplantation with loss of graft function in half of affected individuals. The efficacy of treatment of FSGS depends on histopathological findings in renal biopsy and clinical presentation, especially on the intensity of proteinuria. There is no uniform standard of therapy for FSGS. A six-month course of steroids and/or cyclosporine A (CsA) as well as ACE inhibitors and/or angiotensin receptor blockers (ARBs) and lipid-lowering agents are recommended. In steroid-dependent patients or those with frequent relapse of proteinuria, cyclophosphamide with prednison should be administered. In steroid-resistant nephrotic syndrome the podocine gene mutation (NPHS2 gene) should be assessed to avoid prolonged and ineffective treatment with adverse effects and evaluation before further kidney allograft transplantation, with a low risk of recurrence in homozygous mutation patients (Adv Clin Exp Med 2008, 17, 2, 221–226).

Key words: FSGS, pathogenesis, treatment, recurrence after kidney transplantation.

Streszczenie

Pierwotne ogniskowe segmentalne stwardnienie kłębuszków nerkowych (FSGS – focal segmental glomerulosclerosis) jest postacią uszkodzenia kłębuszków nerkowych o niecałkowicie wyjaśnionej etiologii, charakteryzującą się ogniskowym (w niektórych kłębuszkach) i segmentalnym (w niektórych pętlach naczyniowych) występowaniem zmian. Uważa się obecnie, że pierwotną przyczyną jest uszkodzenie komórek nabłonka trzewnego kłębuszków nerkowych (podocytów). FSGS jest jedną z najczęstszych przyczyn zespołu nerczywego u osób dorosłych. Značający wpływ na przebieg choroby ma nasilenie białkomoczu i utratę filtracji kłębuszkowej w momencie rozpoznania. Rokowanie w FSGS jest zło ze względu na brak samoistnych remisji i częstą oporność na leczenie. FSGS często nawraca w nerce przeszczepionej, powodując utratę czynności nerki przeszczepionej u około połowy chorych. Skuteczność leczenia FSGS zależy od postaci histopatologicznej i obrazu klinicznego, szczególnie od nasilenia białkomoczu. Nie ma jednej ustalonej standardowej terapii FSGS. Rekomendowane jest 6-miesięczne leczenie steroidami i/lub cyklosporyną A (CsA), jak również inhibitorami enzymu konwertującego (IEK) i/lub lekami blokującymi receptor angiotensyny (ARB) oraz statynami. U pacjentów steroidozałożnych lub przy częstym nawrocie białkomoczu jest wskazane leczenie cyklofosfamidem wraz ze steroidami. W steroidozałożnym zespole nerczywym należy poszukiwać mutacji genu dla podocyny (NPHS2), aby uniknąć długotrwałego a nieskutecznego leczenia z jego możliwymi objawami ubocznymi i ocenić ryzyko nawrotu po przeszczepieniu nerki, które w postaci homozygotycznej jest niskie (Adv Clin Exp Med 2008, 17, 2, 221–226).

Słowa kluczowe: FSGS, patogeneza, leczenie, nawrót po przeszczepieniu nerki.

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Focal segmental glomerulosclerosis (FSGS) 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, the formation of adhesions between the glomerular tuft and Bowman’s capsule, and podocyte hypertrophy. The most likely mechanism seems to be podocyte injury. Although the idiopathic form of FSGS is the most common, FSGS can also occur in association with reflux nephropathy, obesity, human immunodeficiency virus or parvovirus B19 infections, as well as pemphigronate therapy or heroin abuse. The clinical hallmarks include proteinuria or nephrotic syndrome (NS) and frequently the progressive loss of renal function. Hypertension is also common. Predictors of progression are the presence of NS as well as elevated serum creatinine concentration at presentation, but erythrocyturia, age, and gender are not.

Pathogenesis of FSGS

The pathogenesis of FSGS is not fully clarified [1], but injury of glomerular epithelial cells (podocytes), probably by circulating vascular permeability factor(s) (VPF), possibly a lymphokine or cytokine (product of activated lymphocytes T), is crucial [2]. The concept of an immune-derived VPF was attributed to Shalhoub’s hypothesis in the early 1970s [3]. Evidence for circulating VPF originates from the clinical observation of recurrence of FSGS in up to 30% of patients after renal transplantation, occasionally within a week. Plasmapheresis and immunoabsorption have been used empirically with success to remove VPFs with disappearance of proteinuria. The recent discovery of mutations of four proteins exclusively expressed by podocytes, i.e. podocin (NPHS1), α actinin-4 (ACTN4), CD2-associated protein (CD2AP), and nephrin (NPHS1) in familial forms of FSGS has shed new light on the pathogenic mechanisms of the disease. Homozygous mutations of podocin (NPHS2) have been associated with sporadic FSGS and is observed in 20–30% of children with steroid-resistant NS and less frequent in late-onset NS in adults [1, 4].

Transforming growth factor β (TGFβ) is probably a mediator of scarring by the induction of apoptosis of podocytes and adherence of parietal epithelial cells to the naked glomerular basement membrane (GBM) [5]. There is evidence that antibodies or inhibitors of TGFβ retard the sclerosing process. In the collapsing and cellular variants of FSGS [6], the dedifferentiation and dysregulation of podocytes with proliferative phenotype are considered in the pathogenesis [7, 8]. Dysregulated podocytes are characterized by loss of maturity markers (Glepp1, synaptopodin, vimentin, podocalixin, WT1, CALLA (CD10), receptor for C3b and CR1 as well as PHM-5) and acquire epitopes characteristic of macrophages (P-cadherin, cytokeratin, PAX2, collagen IVα1 and α2, KP1, PG-M1, M18, and CD68) [9, 10], but normal podocytes are considered terminally differentiated post-mitotic cells which are unable to proliferate and to compensate for damaged neighboring podocytes [11].

Diagnosis

FSGS is not a disease entity, but rather a pattern of injury [11]. Recently, five morphological variants have been defined in biopsy findings with focal and segmental localizations [12]: 1) the perihilar variant (lesions located predominantly at the vascular pole), 2) the tip variant (lesions located at the urinary pole) [13], 3) the cellular variant (with endocapillary hypercellularity), 4) the collapsing variant (with collapse of the glomerular tuft associated with epithelial cell hypertrophy and hyperplasia), and 5) FSGS not otherwise specified [11]. All morphologic variants are accompanied by some degree of epithelial proliferation [11]. The criteria requires the presence of areas of glomerular sclerosis or tuft collapse that were both focal (involving only a subpopulation of glomeruli) and segmental (spARING portions of involved glomeruli) with segmental hyalinosis present in several cases. A lesion involves some of the glomeruli in the biopsy with others remaining uninvolved. The collapsing variant is associated with a poor response to therapy, rapid loss of renal function, and progression to end-stage renal disease (ESRD) [6], the tip lesion [13] with marked proteinuria and relatively good response to treatment, and the perihilar variant with the presence of synechiae with the Bowman’s capsule [11]. Accumulation of extracellular matrix (ECM) proteins and foam cells leads to capillary tuft collapse and an increase in collagen deposits accompanied tubulointestinal fibrosis. The exact histological diagnosis is sometimes difficult because sclerotic lesions are usually confined to only a few glomeruli in the juxtaamedullary area. Because the glomerular changes are focal, and the remaining glomeruli are uninvolved in light microscopy, there is the possibility to misdiagnose minimal-change disease (MCD) instead of FSGS, especially with no confirmation in immunofluorescence (IF) and electron microscopy. Examination of the urinary excretion of podocytes can be a noninva-
sive test that might help distinguish active FSGS from MCD (especially in the NS of childhood in the absence of renal biopsy). Podocytes are detected by IF using monoclonal antibodies against the podocalyxin (anti-PCX); in FSGS there are significantly more urinary podocytes than in minimal-change disease [14, 15]. Ancillary factors supporting the diagnosis of FSGS, including the detection of focal, segmental glomerular staining for immunoglobulin M and/or C3 and C1q by immunofluorescence, are appropriate. Careful electron microscopy examination reveals effacement of the podocyte foot processes, outward bulging of the thickening of the GBM, and subendothelial deposits in areas of hyalinosis.

**FSGS Recurrence After Kidney Transplantation**

FSGS has a high recurrence rate after kidney transplantation, reaching approximately 15–50% in the first kidney transplant and as much as 80% in the second [16]. The risk of recurrence differs in children and adults (50% vs. 11%, respectively) [17]. Recurrence is more frequent in kidney allograft recipients with a serious course of FSGS in the native kidneys (with mesangial proliferation) and fast progression to ESRD [16]. Among patients with a homozygous NPHS2 mutation, a molecular defect of podocin is considered to be the disease-causing mechanism. Since this mechanism should have vanished after kidney transplantation, patients bearing homozygous mutations are at low risk of FSGS recurrence, with only the possibility of other proteinuria-inducing factors (i.e. VPF or autoantibodies against unmutated podocin) [18]. In these circumstances, massive proteinuria may develop even in the first day after transplantation, with imminent loss of kidney allograft function. Increased immunosuppressive dosage and repeated sessions of plasmapheresis or plasma protein adsorption on columns coated with staphylococcal protein seemed to partially control an unfavorable evolution.

**Treatment**

Treatment of FSGS in adults depends on histopathological findings in renal biopsy and clinical presentation, especially on the intensity of proteinuria. Treatment with ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB) with optimal blood pressure control might be advised only in patients with mild proteinuria, as well as restrictions of dietary protein (to 0.8 g/kg/day) and salt (to 50–100 mmol/day or 2.9–5.8 g NaCl/day) intake. It would be of no avail to treat mildly proteinuric FSGS with steroids. In nephrotic-range proteinuria, corticosteroids remain the mainstay of treatment. It is now established that corticosteroid treatment must be sufficiently long, at last 6 months. In mildly intense NS it is advised to use oral prednisone at an initial dose of 0.8–1.0 mg/kg/day. Taking into account steroid side-effects and toxicity, a full-dose prednisone (about 60 mg/day) is given for 2–3 months with complete remission in 25–40% of patients, with further prednisone 0.8 mg/kg every second day for the next 4–6 months. In case of even partial remission, a slowly tapering dose over months should be advised to avoid a rebound effect. Nonetheless, reducing proteinuria, even partially, is the only means of slowing or arresting the progression to ESRD. Lack of remission after 4 months of steroid treatment is the basis for diagnosing steroid-resistant NS. In heavy NS, remission should be induced by intravenous pulses of methylprednisolone (0.5 g per day on three consecutive days) and further oral prednisone (mg/kg/day) for 3 months, with later reduction to 0.5 mg/kg/day. Lack of even a partial remission after 4 months of steroid treatment justifies adding cytotoxic alkylating agent. Besides prednisone (0.5 mg/kg /day), oral cyclophosphamide (CPD) is recommended, initially at a dose of 2 mg/kg/day, with reduction after 2 months to 1.0–1.5 mg/kg/day). After achieving a total dose 60–80 mg/kg, CPD should be replaced by oral azathioprine (AZA) at a dose of 1 mg/kg/day, even for 2 years. The main advantage of cytotoxic agents is that the remission they yield is long lasting.

**Recurrence, Steroid-Dependent and Steroid-Resistant FSGS**

Symptoms of FSGS relapse in nearly half of patients with previous remission, and also in some others during the tapering of the steroid dose (steroid-dependent FSGS). In these cases, CPD and cyclosporine A (CsA) are advantageous, with induction of complete or partial remission in about ¾ of patients. There is consistent evidence that CsA diminishes or abolishes proteinuria by two different mechanisms: its immunosuppressive action and what appears to be a non-immunological effect. Nowadays, steroid resistance is established when six months of steroid treatment is ineffective; this involves about 50% of those treated. Complete or partial remission is to be obtained in 1/5 of them with prednisone (0.5 mg/kg every second day) and CsA (initially 5.0–6.0 mg/kg/day).
in two divided doses), and then adjusted to the trough whole blood level (recommended: 125–200 ng/ml) [19]. High serum cholesterol levels in NS should be taken into account to adapt the dosage because it is likely that part of the highly lipophilic CsA molecule is bound to serum lipids and that the active moiety is low. Nevertheless, after stopping CsA, especially before 6 months, NS recurred. CsA is now considered amongst the most useful agents in the treatment of NS in FSGS. Based on these findings, prolonged treatment, even for 12 months, with CsA is advised with a very slow tapering of the CsA dosage, although this promoted interstitial fibrosis [20]. The reduction of proteinuria is attributed to renal vasoconstriction. Some experience in the treatment of steroid-resistant FSGS has been reported with tacrolimus, another calcineurin inhibitor, initially at a dose of 0.15–0.1 mg/kg/day in two divided doses and adjusted to the recommended trough blood level (5–10 ng/ml) for the next 6 months. Complete remission was achieved in 40% of patients and a high relapse rate (76%) after discontinuation [21]. Tacrolimus may induce complete remission in some cases and fail in others. A favorable effect of mycophenolate mofetil (MMF, 2 g/day, in 2 divided doses) was observed in few groups of patients [22, 23], but large-scale studies are lacking. In others both MMF and tacrolimus, used in a few limited groups of patients with steroid-resistant FSGS, had low efficacy. In some patients with FSGS, sirolimus (a target of rapamycin inhibitor) is efficacious in reducing proteinuria, with partial or complete remission in 57% of patients and with no long-term nephrotoxicity [24].

**Treatment of FSGS in Kidney Allograft**

Because the recurrence of FSGS may be an effect of a so far unidentified lymphokine (VPF) derived from T cells, high doses of CsA and plasmapheresis should be administered, with an exchange of 60 ml of plasma for every 1 kg b.w. per session. Plasmapheresis is done at first 2–3 times a week and then once every 2–4 weeks, with about 50% efficacy, and sometimes better with early start during the first month after recurrence [20]. Immunoabsorption on columns with protein A has similar efficacy [25]. In heavy NS with fast progress toward ESRD, a closely related living donor kidney transplantation should be avoided because of the high risk of allograft loss. The genetic assessment for an NPHS2 mutation should be proposed to the candidate relative donor because of the higher susceptibility of the graft to injury in the case of asymptomatic heterozygous NPHS2 mutation.

**Prognosis**

In the last 20 years the results of therapy have improved, especially with prolonged (6–9 months) corticosteroid therapy. The efficacy of treatment depends substantially on the histopathological FSGS variant. Tip lesions, predominant in Caucasians, have relatively good response to steroid treatment, but the collapse variant has a more serious clinical course, steroid resistance, and rapid progression to ESRD (within 2 to 3 years) [26]. Prednisone for longer than 16 weeks gives better results, with complete remissions in 35–45% and partial remission even in 61% of the patients of the group described by Ponticelli et al. [27]. The relapse of NS in idiopathic FSGS may respond to a second course of steroids. The efficacy of steroids in NS (1 mg/kg/day) for 3–4 months and then with slow tapering for 2–3 months in complete or partial remission patients or faster (4–6 weeks) in nonresponders. The complete or partial remission rates obtained in the perihilar, collapsing, and tip lesions variants were 53, 64, and 78%, respectively, but the differences were below significance. All patients with remission in the classical FSGS (perihilar) and tip lesion variants as well as 80% of patients with the collapsing variant had good prognosis and no renal insufficiency after 10 years. A necessary condition for efficacy in the collapsing variant was the early initiation of therapy; the collapsed capillary tufts in ≥ 20% of glomeruli was connected with significantly worse response to steroids and poor prognosis [28]. In steroid-resistant NS, the alternative therapy is CsA, most beneficial with a low dose of prednisone [26]. Complete and partial remissions were achieved in 29% and 22% and failure in 49% of those treated [26]. To maintain the remission the prolonged (sometimes over 18 months), low dose (< 3 mg/kg/day) CsA therapy for several years may be necessary. The overall prognosis is poor; despite therapy, 27% of patients after 5 years and 50% after 10 years need renal replacement therapy. Better prognosis is for patients with retained GFR and no nephrotic range proteinuria; about 80% of them have no ESRD in over 10 years, whereas half of NS patients develop ESRD in 5 years. The most serious course is observed in massive proteinuria (> 10 g/day) and mesangial proliferation with focal and segmental sclerosis, where almost all patients develop ESRD in 3 years. In complete and partial remission of NS, the risk of progression to ESRD in 5 years diminished to 2% and 15%, respectively.
The authors concluded that there was no uniform standard of therapy for FSGS. Six-month courses with steroids and/or CsA as well as with IACE and/or ARB and lipid lowering agents are recommended, with remission in about 50% of patients. There is no established role of tacrolimus and MMF in treatment. Symptomatic treatment is allowed only with preserved filtration rate (with normal GFR) and subnephrotic proteinuria, while high doses of prednisone (1 mg/kg/day) for a minimum of 16 weeks are recommended for others. In steroid-dependent patients or those with frequent relapse of proteinuria, CPD with prednisone should be administered. In steroid-resistant FSGS the most effective treatment is based on CsA for 6 months, but this should be reserved only for patients with proper GFR to avoid nephrotoxicity. In patients with remission the treatment is to be continued for up to one year, with tapering of the doses and discontinuation after 6 months in non-relapsed individuals. In steroid-resistant NS in children and young adults (< 35 years), defined as no remission after steroid treatment for 6 weeks in children and 12–16 weeks in adults, the podocine gene mutation (NPHS2 gene) should be assessed to avoid prolonged treatment with its adverse effects and evaluation before further kidney allograft transplantation because of the low risk of recurrence in homozygous mutation patients.

References

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