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REVIEW

Review on diagnosis and treatment of focal segmental glomerulosclerosis

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is one the most important causes of the nephrotic syndrome in adult patients. FSGS is not a disease entity. The identification of underlying causes of FSGS (secondary FSGS) has increased our insight into the pathogenesis of FSGS. Moreover, differentiating between primary (idiopathic) and secondary forms of FSGS is important to allow appropriate treatment. Recently a new pathological classification of FSGS was proposed, expanding FSGS to include nonsclerotic lesions. In this review we discuss the current diagnostic and therapeutic options in patients with FSGS.

KEYWORDS

Diagnosis, focal segmental glomerulosclerosis, nephrotic syndrome, treatment

INTRODUCTION

In 1957, Rich provided the first detailed pathological description of focal segmental glomerulosclerosis (FSGS).[1] However, it was not until the 1970s that FSGS emerged as a separate clinico-pathological entity.[2] Currently, FSGS is one of the most common patterns of glomerular injury encountered in human renal biopsies.[3] For a long period of time FSGS in adults has been considered to be prednisone resistant.[4] However, over the last 25 years the results of treatment have improved. Furthermore, new underlying causes of FSGS have been identified and improved our understanding of the pathogenesis of FSGS. Moreover, a recently proposed pathology classification has pointed to the existence of new, nonsclerotic forms of FSGS. In this review, we provide an update on the diagnosis and treatment of FSGS.

Aetiology and pathogenesis of FSGS

According to the classical description, FSGS is characterised by the presence of a scarring lesion in a portion (segment) of some (focal), but not all glomeruli. The scar comprises increased mesangial matrix with collapsed glomerular capillaries, an adhesion between the tuft and Bowman's capsule, and hyaline deposits.[5] The glomerular scar can be accompanied by features such as mesangial hypercellularity and foam cells. Progressive lesions are characterised by periglomerular and tubulo-interstitial fibrosis.

It has been recognised for many years that FSGS is a merely descriptive diagnosis and not a single disease entity. FSGS can be idiopathic (primary; unknown cause) or secondary (with underlying cause). Secondary forms of FSGS were generally considered to result from maladaptive responses that occurred due to the loss of functioning nephrons, hyperfiltration or increased glomerular pressure. Based on studies in experimental animal models such as the remnant kidney model in the rat, Kriz *et al*. demonstrated that loss of podocytes was pivotal in FSGS resulting from these maladaptive responses.[6] Of note, all animal models used had evidence of glomerular hyperfiltration, hypertrophy or increased glomerular pressure. Based on these studies Kriz proposed that the following sequence of events results in FSGS: there is initial injury to the podocyte, the damaged podocytes detach from the glomerular basement membrane (GBM), ultimately followed by loss of the entire cell into Bowman's space. Because podocytes are incapable of regenerative replication, loss of podocytes cannot be replaced, which leads to areas of 'bare' GBM. Next, parietal epithelial cells covering Bowman's capsule attach to the bare GBM, leading to the formation of an adhesion between the capillary tuft and Bowman's capsule. At the site of the adhesion, a gap forms in the parietal epithelium. If the

attached capillary is still functioning, fluid leaks into the gap in the parietal epithelium (misdirected filtration), leading to the formation of a fluid-rich periglomerular space. Then fibroblasts are stimulated, which results in periglomerular and tubulointerstitial fibrosis. The continuing misdirected filtration and podocyte loss results in a further expansion of the adhesion. Inside an adhesion capillaries eventually collapse or become occluded either by deposition of hyaline material or microthrombosis.

In recent years the list of secondary causes has steadily grown and now also includes FSGS not related to glomerular hyperfiltration (*table 1*). FSGS may result from direct injury to the podocytes due to viral infections (HIV) or the use of drugs (pamidronate/alendronate).[7,8] Even more important, and instrumental in our knowledge of the role of the podocyte in proteinuria and FSGS, was the discovery that Finnish type congenital nephrotic syndrome was caused by mutations in nephrin, a podocytic protein and important constituent of the slit diaphragm.[9] Meanwhile, mutations in other podocytic proteins have been discovered in other familial forms of FSGS (*table 1*). A special form of inheritable FSGS is caused by podocytic mitochondrial DNA mutations.[10]

Still, for most patients with FSGS the pathogenesis is still unknown. There is strong evidence that this idiopathic FSGS may be the result of a circulating factor that alters the permeability of glomeruli.[11,12] The best evidence supporting the presence of a circulating factor comes from recurrent FSGS after renal transplantation. Proteinuria may develop within days after transplantation, and plasma exchange instituted early in the course of recurrent disease removes the putative factor and results in a remission of proteinuria.[13] More recent data paint a more complicated picture, suggesting that the increased permeability may be due to the absence or loss of an inhibitor for the permeability factor.[14]

Damage to the podocyte also plays a central role in the pathogenesis of idiopathic FSGS.[15] However, the subsequent events differ from secondary FSGS due to maladaptive responses.

Based on studies in animals and humans we proposed the following sequence of events in idiopathic FSGS.[16-18] Initially injury of the podocytes results in foot process effacement, proteinuria and microvillous transformation without podocyte detachment or podocyte loss. Parietal epithelial cells (PECs) are injured, start to proliferate and cover the glomerular tuft. The proliferating PECs produce and deposit newly formed extracellular matrix that leads to scarring. The stimulus for PEC proliferation is not clear. Possibly, the interaction between activated/injured podocytes and activated/injured PECs or denuded areas of Bowman's capsule plays a role.[19]

Table 1. *Aetiological classification of focal segmental glomerulosclerosis (FSGS)*[101]

Idiopathic (primary) FSGS
Secondary FSGS:
1. Familial
   - A. Mutations in α-actinin 4
   - B. Mutations in nephrin
   - C. Mutations in podocin
   - D. Mutations in WT-1
   - E. Mutations in CD2-associated protein
   - F. Mitochondrial cytopathies
2. Virus associated
   - A. HIV-associated nephropathy
   - B. Parvovirus B19
3. Medication
   - A. Heroin nephropathy
   - B. Interferon-α
   - C. Lithium
   - D. Pamidronate / alendronate
4. Adaptive structural-functional responses likely mediated by glomerular hypertrophy or hyperfiltration
   - 4.1 Reduced renal mass
     - A. Oligomeganephronia
     - B. Unilateral renal agenesis
     - C. Renal dysplasia
     - D. Cortical necrosis
     - E. Reflux nephropathy
     - F. Surgical renal ablation
     - G. Chronic allograft nephropathy
     - H. Any advanced renal disease with reduction in functioning nephrons
   - 4.2 Initially normal renal mass
     - A. Diabetes mellitus
     - B. Hypertension
     - C. Obesity
     - D. Cyanotic congenital heart disease
     - E. Sickle cell anaemia
5. Malignancy (lymphoma)

Nonspecific pattern of FSGS caused by renal scarring in glomerular disease
- A. Focal proliferative glomerulonephritis (IgA nephropathy, lupus nephritis, pauci-immune focal necrotising and crescentic glomerulonephritis)
- B. Hereditary nephritis (Alport syndrome)
- C. Membranous glomerulopathy
- D. Thrombotic microangiopathy

DIAGNOSIS OF IDIOPATHIC AND SECONDARY FSGS

Distinguishing between idiopathic and secondary forms is not merely semantic, but has important therapeutic implications as discussed below. Generally, the distinction can be made from the history (with special attention to secondary causes) and some additional laboratory (serum albumin) and radiological (chest X-ray and kidney ultrasound) studies.

In patients with nephrotic range proteinuria (≥3 g/day), serum albumin is an important clinical parameter to distinguish between FSGS secondary to hyperfiltration and other forms of FSGS. In a study of 37 patients with nephrotic range proteinuria due to biopsy-proven FSGS, Praga *et al.* showed that serum albumin was significantly lower in patients with presumed idiopathic FSGS (serum albumin <30 g/l) compared with FSGS

secondary to massive obesity, vesicoureteral reflux, or renal mass reduction (serum albumin >35 g/l).[20] In contrast to hyperfiltration-associated FSGS, other forms of secondary FGSG such as viral-associated FSGS, drug-induced FSGS and familial FSGS may also present with a low serum albumin. Especially the last-mentioned form cannot be differentiated from idiopathic FSGS on clinical grounds.

Although clinical data and serum albumin levels often allow differentiation between idiopathic FSGS and FSGS secondary to hyperfiltration, discussion sometimes remains, especially in patients with a serum albumin between 30 g/l and 35 g/l. It has been suggested that these forms could be differentiated by evaluation of foot process effacement in electron microscopy, with mild effacement occurring in secondary FSGS and complete effacement in idiopathic FSGS.[21,22] In a recent study of podocyte alterations we noted that the mean foot process width was significantly greater in patients with idiopathic FSGS compared with secondary FSGS mediated by adaptive structural-functional responses.[23] The association between foot process width and type of FSGS was independent of proteinuria. Furthermore, the degree of overlap in foot process width between idiopathic and secondary FSGS was low, suggesting that quantitative assessment of foot processes may provide a means for distinguishing between idiopathic and secondary FSGS. Electron microscopy can also help in determining other underlying causes of FSGS. Special attention should be paid to the presence of tubulo-reticular inclusions in endothelial cells (HIV), viral particles, or the presence of abnormal mitochondria in the podocyte (mitochondrial DNA mutation).

A positive family history identifies patients with FSGS based on mutations in podocytic proteins.[24-26] Obviously, it is important to consider whether patients with FSGS need genetic testing to evaluate spontaneous mutations. In contrast to children, spontaneous mutations in adults with FSGS are rare, with a reported prevalence of 1.5 to 5%.[27-29] He *et al.* screened 78 adult patients with nonfamilial FSGS (15 steroid-sensitive and 63 steroid-resistant) for known mutations in the podocin gene. Compound heterozygous mutations were detected in only one patient with steroid-sensitive FSGS; no homozygous mutations were found. These results are consistent with the findings by Caridi *et al.,* who discovered only three heterozygous mutations in a cohort of 64 patients with steroid-resistant nephrotic syndrome.[28] The study by He *et al.* also identified eight patients with heterozygous R229Q, a podocin polymorphism. The allele frequency of this variant did not differ from normal controls. The significance of the R229Q variant as a disease-causing mutation in FSGS is currently unknown.[30] Similarly, mutations in the gene encoding α-actinin-4 are also rare. Aucella *et al.* found no α-actinin-4 gene mutations in 33 adults with nonfamilial FSGS.[29] In view of the low incidence of spontaneous mutations, we do not recommend mutation screening in adult patients with nonfamilial FSGS.

CLINICAL PRESENTATION, PROGNOSIS AND TREATMENT

The data on the clinical characteristics and natural history of patients with FSGS are biased by variable inclusion criteria of the reported studies. Patients with secondary FSGS due to hyperfiltration injury will not be biopsied and are often not included in these studies. Search for aetiological causes has been limited, especially in the older studies. In most studies patients with idiopathic FSGS will predominate.

Clinical presentation

FSGS can occur at any age. In adults the mean age at onset varies between 40 and 50 years.[31-33] The number of affected males and females is roughly similar with a male-to-female ratio of 1:1. Patients with idiopathic FSGS and patients with FSGS secondary to infections, medication or genetic mutations typically present with a nephrotic syndrome.[20] By comparison, patients with FSGS secondary to adaptive structural-functional responses (hyperfiltration-associated FSGS) usually present with a more indolent course without hypoalbuminaemia or oedema, even when proteinuria exceeds 3 to 4 g/day.[20,22] In addition to proteinuria, microscopic haematuria and hypertension are common presenting features of both idiopathic and secondary FSGS.

Prognosis

Important clinical features predicting the clinical course of FSGS are the amount of proteinuria and the level of plasma creatinine. Half of the patients presenting with a proteinuria >3 g/day or a serum creatinine over 115 μmol/l progress to end-stage renal disease within five to ten years.[34-36] Renal survival is even worse if proteinuria exceeds 10 g/day, with end-stage renal disease (ESRD) occurring in the majority of patients within five years after presentation. In contrast, non-nephrotic proteinuria portends a much better prognosis, with a renal survival of >80% after ten years. Still, the single best predictor of a favourable outcome is attainment of a complete or partial remission of proteinuria. Less than 15% of patients attaining a remission progress to ESRD.[33,37,38] Most reported remissions were induced by steroid therapy and it is generally suggested that spontaneous remissions occur infrequently in patients with FSGS. However, we have recently shown a high spontaneous remission rate of 60% in patients with idiopathic FSGS who present with a normal renal function and a selective proteinuria (selectivity index <0.2). In addition these patients were characterised by a serum albumin >20 g/l and a proteinuria <8 g/day at three months after renal biopsy.[39]

Other authors have attempted to determine whether prognosis in patients with FSGS can be predicted. Bazzi

et al. showed that a fractional excretion (FE) of IgG <0.14% was associated with a high remission rate after immunosuppressive therapy.[40] In contrast, patients with an FE of IgG >0.14% had a dismal prognosis even with immunosuppressive therapy. Recently, we also reported on the predictive value of FE IgG in 32 patients with idiopathic FSGS.[41] Our data do not support Bazzi's conclusion that FE IgG predicts resistance to immunosuppressive medication. Although an FE IgG >0.14% was associated with worse baseline characteristics, remission rate was high (59%) and not different from patients with FE IgG <0.14%. Therefore, until more data become available, FE IgG should not be used to guide treatment in patients with FSGS.

Approximately 50% of patients who develop a remission after prednisone therapy will develop recurrent proteinuria during tapering of the prednisone (steroid dependent) or after stopping treatment (relapse). Patients who do not develop a remission after a minimum of eight to 16 weeks of prednisone therapy are called steroid resistant. However, this definition is subject to debate (see below).

Treatment

In patients with secondary FSGS, therapy should obviously be directed at the underlying disorder or removal of the inciting drug. In patients with severe obesity, weight loss (>10% of body mass index) induces a significant decrease of proteinuria, which is almost similar to the effect of ACE inhibitors.[42] However, maintaining the weight loss is often difficult and many patients relapse.[43] Small cohort studies suggest that antiretroviral therapy improves renal survival in patients with HIV-associated FSGS.[44,45] Case reports also provide support for the use of antiretroviral therapy, with recovery of dialysis-dependent renal failure after initiation of antiretroviral therapy.[46] FSGS associated with haematological conditions such as multiple myeloma and (non) Hodgkin's lymphomas often responds with a resolution of the proteinuria after successful treatment of the underlying haematological condition.[47,48] Familial forms of FSGS are known to be steroid resistant.[25,49-51] A possible exception are patients with a nonfamilial (sporadic) heterozygous podocin mutation.[52]

It is well known that blood pressure control and reduction of proteinuria significantly slows the progression of renal insufficiency in patients with proteinuric nondiabetic renal disease.[53-57] Proteinuria should be reduced to <0.5 g/day. Target blood pressures are ≤130/80 mmHg in patients with proteinuria ≤1 g/day and ≤125/75 mmHg in patients with proteinuria >1 g/day.[55,58] ACE inhibitors (ACE-i) or in case of side effects angiotensin receptor blockers (ARB) are preferred because they are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases.[53,58,59] Despite the recognised beneficial effect of ACE-i in patients with chronic kidney disease, little is known about the efficacy of ACE-i in patients with idiopathic FSGS. Although ACE-i reduce proteinuria in idiopathic FSGS, the few available studies suggest that ACE-i rarely induce a complete remission and development of end-stage renal disease is not prevented.[60,61] However, there is some evidence that ACE-i slow the progression to ESRD.[62] Furthermore, treatment with ACE-i also improves the hypoalbuminaemia and hyperlipidaemia that is associated with idiopathic FSGS.[63] Therefore, treatment with ACE-i is recommended for all patients with FSGS. The antiproteinuric effect of ACE-i is most prominent in patients who are on a low sodium diet (50 to 100 mmol/day) or who are treated with diuretics, since relative volume depletion results in greater angiotensin II dependence of the glomerular microcirculation. Other antihypertensive drugs should be added if the goals for blood pressure and proteinuria are not reached with ACE-i, a low sodium diet and diuretics.

An abnormal lipid metabolism usually accompanies a nephrotic syndrome. Most prominent are an increased LDL cholesterol, hypertriglyceridaemia and an increased lipoprotein A (LP(a)).[64,65] This combination is highly atherogenic.[66,67] HMG CoA reductase inhibitors (statins) are very effective in lowering total and LDL cholesterol and to a lesser degree triglycerides and LP(a), also in patients with a nephrotic syndrome.[68-72] Although a cardioprotective effect of statins has never been proven in patients with a nephrotic syndrome, prevention studies in the general population with similar lipid disorders have shown a marked reduction of cardiovascular diseases.[73,74] Notably, recent studies have also suggested that the use of statins in patients with proteinuria attenuates the deterioration of renal function.[75,76]

Immunosuppressive therapy should be considered in patients with idiopathic FSGS and a proteinuria ≥3 g/day. Current recommendations for the initial treatment of idiopathic FSGS are almost entirely based on retrospective studies.[38] Data from these studies show that corticosteroids remain the mainstay of treatment in idiopathic FSGS. Remission rates do not improve if cytotoxic agents are added to the initial treatment of FSGS with corticosteroids.[77] To attain a remission both the duration and dose of corticosteroid therapy are important factors. The median time until a remission is attained is three to four months, with the majority of patients entering a remission within six months.[34,35,77-82] In addition, studies reporting higher remission rates are also characterised by a longer duration (two to four months) of high-dose treatment.[35] FSGS is often considered to be steroid resistant if no remission has occurred after two to four months of treatment with high-dose prednisone.[83] However, a significant number of patients do attain a remission four to six months after initiation of treatment with high-dose prednisone. It is our experience that patients who will

eventually develop a remission show some reduction in proteinuria within the first months of treatment. Therefore, one could argue that patients who respond to treatment with a significant reduction of proteinuria (>50%) should be treated for a total of six months before considering them resistant to corticosteroids.[84,85]

Few studies have addressed the best therapeutic approach for relapsing or corticosteroid-dependent FSGS. The most important goal is to achieve a stable remission without the need for long-term prednisone. Both cyclophosphamide and cyclosporine appear to be beneficial, inducing a new remission in 78 and 73% of patients, respectively.[38] However, despite similar remission rates, a new relapse is more common after cessation of cyclosporine. In contrast, cyclophosphamide induces more stable remissions.[86] Cyclophosphamide is usually given in a dose of 2 mg/kg/day for two to three months.

Several studies have evaluated the effect of cytotoxic agents and cyclosporine in patients with corticosteroid resistant FSGS. The definition of steroid resistance was quite variable in these studies, ranging from four to 16 weeks of treatment with prednisone. Alkylating agents do not seem to benefit patients with steroid-resistant FSGS. Retrospective studies in adults report low remission rates for alkylating agents compared with cyclosporine (11 *vs* 40%).[78-80,87-96] Two prospective trials have been conducted in adults, comparing six to 12 months of treatment with cyclosporine with placebo.[91,92] Remission rate was significantly higher in patients treated with cyclosporine (60 to 69%) compared with placebo (4 to 33%). However, within one year after discontinuation of cyclosporine, 60 to 80% of the patients had relapsed.

The high relapse rate may decrease with prolonged use of cyclosporine. A study by Meyrier *et al*. suggests that continuing treatment with cyclosporine for one year in case of a remission followed by a slow tapering of the dose results in a more durable remission.[83] However, this study included a small number of patients with FSGS with relatively mild FSGS lesions on the first renal biopsy. Therefore, the results should be interpreted with caution.

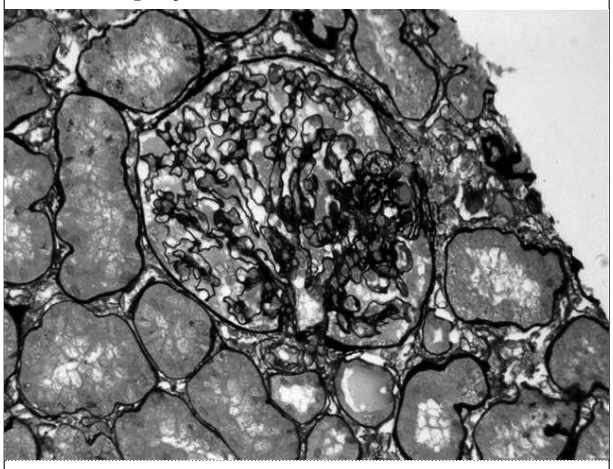
A major concern is the nephrotoxicity of cyclosporine. Continuous use for more than 12 months is associated with a significant increase in tubulointerstitial fibrosis. In most cases serum creatinine does not significantly change despite the aggravation of fibrosis.[83] In addition, cyclosporine may accelerate the progression of FSGS. The number of glomeruli with sclerotic lesions increases significantly during treatment with cyclosporine, even in patients with a partial or complete remission. Cyclosporine nephrotoxicity is associated with higher doses of cyclosporine (>5.5 mg/kg/day), a higher percentage of glomeruli with FSGS lesions and renal insufficiency prior to treatment. Therefore, the cyclosporine dose should not exceed 5.5 mg/kg/day and treatment with cyclosporine should be limited to patients with a creatinine clearance >60 ml/min/1.73 m^2).[83]

Uncontrolled studies have demonstrated an improvement in both renal function and proteinuria for patients with HIV-associated FSGS treated with corticosteroids.[97-99] The data from these studies are conflicting regarding increased risk for serious infections and hospitalisation. Nevertheless, a recent guideline for the management of chronic kidney disease in HIV-infected patients advised considering prednisone therapy at 1 mg/kg/day (maximum dose 80 mg/day) for two months, followed by two to four months taper in patients with HIV-associated FSGS whose kidney function is deteriorating despite use of antiretroviral therapy.[100] Before considering corticosteroids active infection and active illicit intravenous drug use should be excluded. In patients with obesity, treatment with corticosteroids can even be detrimental, because of a further increase in body weight.

A NEW PATHOLOGICAL CLASSIFICATION OF FSGS

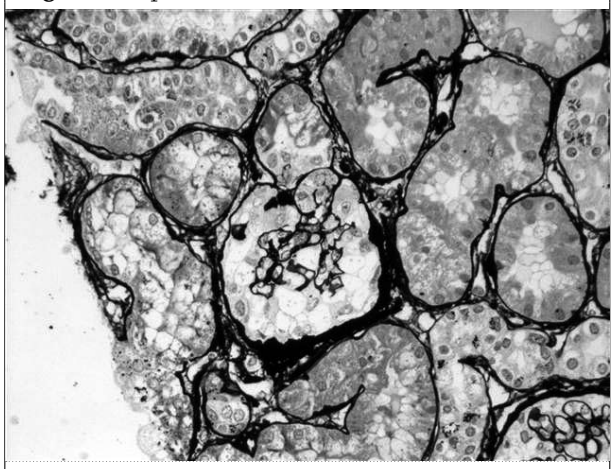
Over the years, the pathological description of FSGS has evolved, and in addition to the classical form other variants have been described. Recently, a group of pathologists proposed a new pathological classification for FSGS based on an assessment of glomerular light microscopic features (Columbia classification; *table 2*; *figures 1* to 5). This classification presumes exclusion of FSGS caused by glomerular scarring in the

Figure 1. *Focal segmental glomerulosclerosis not otherwise specified*



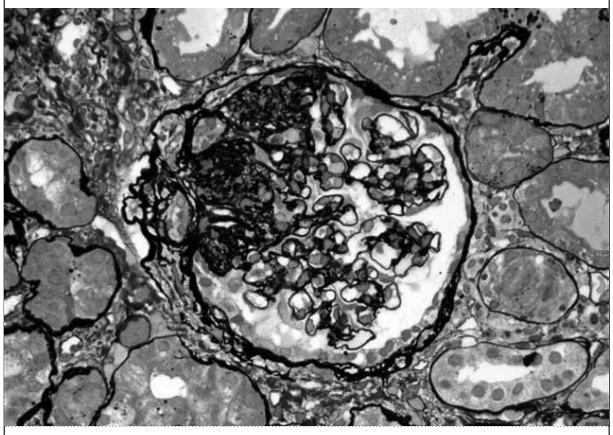
Segmental obliteration of capillary lumina by accumulation of matrix and hyalinosis. Features of collapse, glomerular tip lesion or endocapillary hypercellularity are not seen.

Figure 2. *Tip variant*



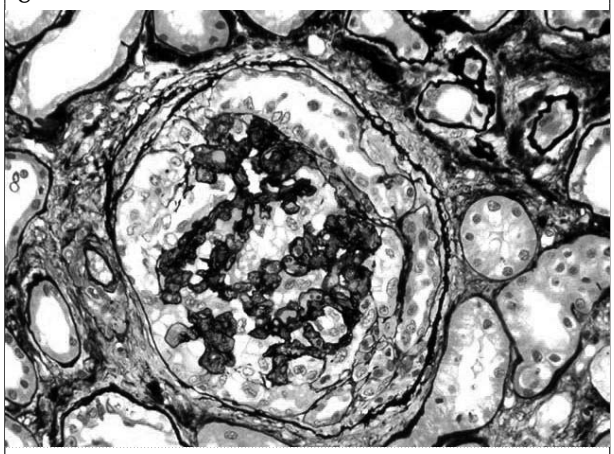
Adhesion between glomerular tuft and Bowman's capsule at the tubular pole, adjacent to the origin of the proximal tubule. No collapse of the capillary tuft.

Figure 3. *Perihilar focal segmental glomerulosclerosis*



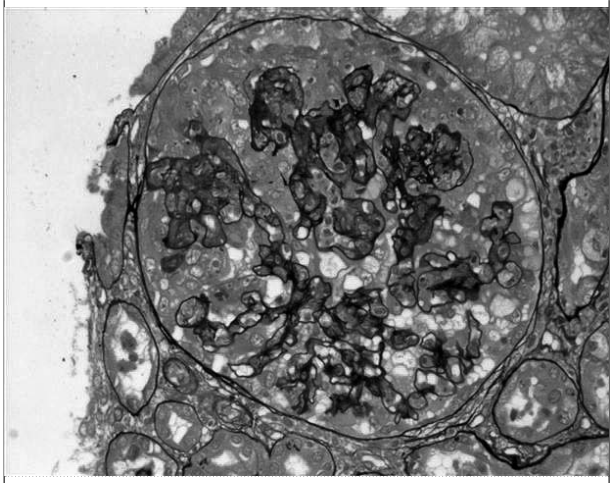
A lesion of segmental sclerosis and hyalinosis located at the glomerular vascular pole. Features of collapse, glomerular tip lesion or endocapillary hypercellularity are not present.

Figure 4. *Collapsing focal segmental glomerulosclerosis*



Global collapse of the capillary tuft, with hypertrophy and hyperplasia of glomerular epithelial cells.

Figure 5. *Cellular focal segmental glomerulosclerosis*



Segmental endocapillary hypercellularity. Features of collapse or glomerular tip lesion are not present.

Table 2. *Morphological variants of focal segmental glomerulosclerosis*[101]

Subtype	Characteristics	Exclusion criteria
Not otherwise specified variant	At least one glomerulus with segmental increase in matrix obliterating the capillary lumen There may be segmental glomerular basement membrane collapse without overlying podocyte hyperplasia	Exclude perihilar, cellular, tip and collapsing variant
Perihilar variant	At least one glomerulus with perihilar hyalinosis, with or without sclerosis >50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis	Exclude cellular, tip and collapsing variant
Cellular variant	At least one glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis	Exclude tip and collapsing variant
Tip variant	At least one segmental lesion involving the tip domain (outer 25% of tuft next to origin of proximal tubule) The tubular pole must be identified in the defining lesion The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck The tip lesion may be cellular or sclerosing	Exclude collapsing variant
Collapsing variant	At least one glomerulus with segmental or global collapse and overlying podocyte hyperplasia	None

course of other idiopathic glomerular diseases (*table 1*).[101] The classification defines five main light microscopic variants: FSGS not otherwise specified (NOS), tip variant, perihilar variant, cellular variant, and collapsing variant. It is important to notice that the presence of sclerosis is no longer obligatory for the diagnosis of FSGS since sclerosis is often absent, particularly in the tip variant and the collapsing variant.

Although the different variants may reflect different diseases (with different causes and differences in pathogenesis), this has not been proven. The different variants may be just a reflection of a different stage of FSGS, dependent on the activity and time of onset of the disease.

Some pathological variants are more likely to occur in relation to certain causes. The perihilar variant of FSGS is associated with hyperfiltration, whereas HIV typically results in collapsing FSGS. However, there is a clear overlap, and patients with idiopathic FSGS may present with either variant.

Clinical presentation and sociodemographic findings differ between the FSGS variants (*table 3*).[32,41,102] Collapsing FSGS has a predilection for black people originating from Africa and typically presents with a severe nephrotic syndrome and substantial renal insufficiency. The tip variant has a low proportion of black people originating from Africa. The majority of these patients also present with a severe nephrotic syndrome (>90%). Renal function is usually preserved in patients with the tip variant. Perihilar FSGS has the lowest frequency of nephrotic syndrome. Patients with FSGS NOS tend to have clinical parameters intermediate between the tip variant and perihilar FSGS, whereas cellular FSGS had clinical parameters intermediate between the tip variant and collapsing FSGS.

Several retrospective studies have reported on the prognostic utility of the Columbia classification. A recent study by Chun *et al*. was unable to detect a significant difference in remission rate among patients with collapsing FSGS, FSGS NOS and the tip variant.[33] However, the statistical power of this study to detect a clinically significant difference was low due to the small number of patients with the tip variant. In contrast, two other studies reported a lower remission rate and worse renal survival among patients with the collapsing variant compared with the tip variant and FSGS NOS.[32,102] Patients with the cellular variant had remission rates between those of patients with the tip variant and collapsing FSGS.[102] A study by our group showed a significantly better renal survival in patients with the tip variant compared with FSGS NOS and perihilar FSGS.[103] These studies suggest that the tip variant has a higher remission rate and a better renal survival compared with other FSGS variants. At present classification of FSGS should not influence therapeutic decisions.

GUIDELINES FOR DIAGNOSIS AND TREATMENT OF FSGS

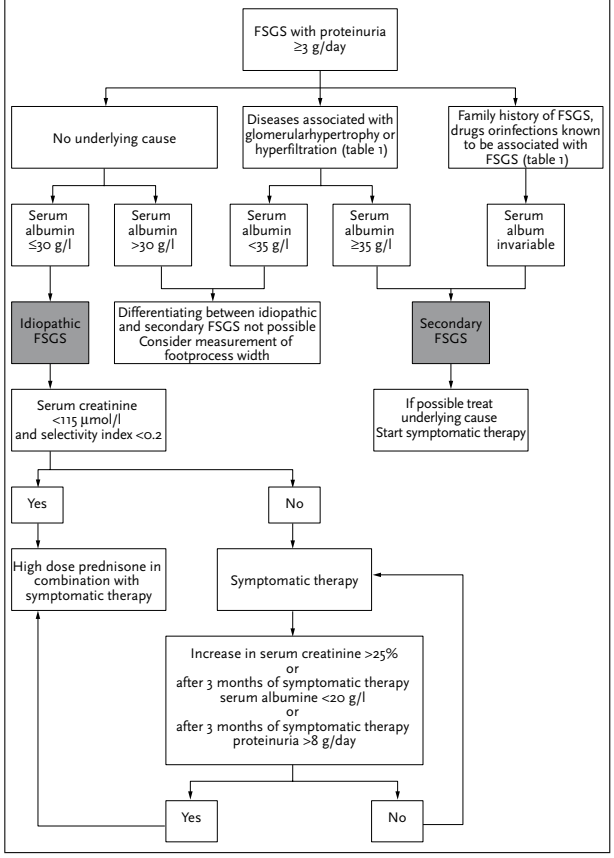
The Dutch Federation of Nephrology recently published guidelines for the diagnosis and treatment of patients with FSGS. An outline of the most important diagnostic steps is given in *figure 6*. Medical history and family history are important to rule out secondary causes of FSGS. We do not advocate routine use of mutational screening. In patients with proteinuria in the nephrotic range (≥3 g/day), serum albumin is an important clinical parameter to distinguish between idiopathic FSGS and FSGS secondary to maladaptive responses. If serum albumin is inconclusive, electron microscopy examination can also help to distinguish between idiopathic FSGS and FSGS secondary to maladaptive responses. Although the use of the Columbia classification is advised for comparative studies, this should

Table 3. *Clinical characteristics of focal segmental glomerulosclerosis variants as reported in two North American and one West-European study*[32,102,103]

	Not otherwise specified (n=200)	Tip (n=128)	Perihilar (n=76)	Collapsing (n=83)	Cellular (n=28)
Male (%)	55%	57%	55%	47%	61%
Age at biopsy (years)	43 ± 5	48 ± 7	50 ± 6	35 ± 4	48 ± 7
Black people	30%	11%	20%	60%	32%
Serum creatinine concentration (μmol/l)	177 ± 91	129 ± 46	166 ± 113	317 ± 133	179 ± 53
Renal insufficiency*	49%	35%	38%	75%	57%
Serum albumin concentration (g/l)	31 ± 5	22 ± 5	37 ± 6	22 ± 5	23 ± 4
Proteinuria (g/24 hours)	5.5 ± 2.9	8.9 ± 3.7	4.7 ± 3.1	9.2 ± 2.7	10.9 ± 4.2
Serum cholesterol	7.3 ± 2.0	8.2 ± 2.1	6.7 ± 1.8	7.7 ± 1.6	6.3 ± 2
Nephrotic syndrome (%)	60%	94%	46%	85%	84%
Mean arterial blood pressure (mmHg)	108 ± 14	111 ± 14	107 ± 13	106 ± 14	110 ± 10
Hypertension (%)	69%	62%	80%	68%	70%

*The definition of renal insufficiency varied between studies, either a serum creatinine >106 μmol/l or >135 μmol/l.

Figure 6. *Flowchart of diagnosis and treatment of focal segmental glomerulosclerosis (FSGS)*



not influence treatment decisions. Immunosuppressive therapy should be limited to patients with idiopathic FSGS. Since spontaneous remissions occur frequently in patients with idiopathic FSGS, normal renal function and a selective proteinuria, a wait-and-see approach should be considered in such patients (*figure 6*). Otherwise, patients with idiopathic FSGS and a nephrotic syndrome should initially be treated with high-dose prednisone for four to six months. To induce a remission, the initial immunosuppressive therapy should consist of high-dose prednisone (1 mg/kg/day, up to 80 mg/day) for four months. In the elderly (>65 years) an alternate day regimen (2 mg/kg/day) is also effective with less complications.[82]

In patients with steroid-dependent or frequently relapsing FSGS, cyclophosphamide 2 mg/kg/day for two to three months in combination with prednisone results in more stable remissions. In steroid-resistant FSGS, the most effective treatment consists of cyclosporine (3-5 mg/kg/day, in two divided doses) for six months. Treatment should be limited to patients with a relatively well-preserved renal function, to prevent nephrotoxicity. If a remission occurs, cyclosporine treatment should be continued for one year and then slowly tapered off to prevent a relapse. In the absence of a remission cyclosporine should be stopped after six months.

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