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Focal and Segmental Glomerulosclerosis

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Abstract Focal and segmental glomerulosclerosis (FSGS) is a common cause of Nephrotic Syndrome in adults. Its most typical course runs from NS to progressive loss of renal function and may recur in the graft after renal transplantation. Current evidence favors prolonged corticosteroid therapy (6 months or longer) to induce remission of proteinuria. Steroid-dependent and steroid-resistant patients may benefit from treatment with cyclosporine or cyclophosphamide. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are effective in reducing proteinuria and are recommended in all patients with FSGS, particularly those with nonnephrotic proteinuria. FSGS can be idiopathic or secondary to glomerular hyperfiltration and high intraglomerular capillary pressure or to viral or toxin-mediated damage. The characteristic lesion is a segmental solidification of the glomerular tuft.

Keywords Focal and segmental glomerulosclerosis · classification · treatment

Introduction

Focal and segmental glomerulosclerosis (FSGS) is a nonspecific pattern of glomerular injury, defined by a segmental solidification of the glomerular tuft owing to collapse of the capillary wall, affecting some glomeruli only. It is one of the main causes of nephrotic syndrome in adults and is characterized by a high incidence of progression to end-stage renal disease. The best predictor of outcome is remission of proteinuria, and because adult nephrotic patients may respond to an aggressive course of corticosteroids, a trial of therapy is recommended. Steroid-dependent and steroid-resistant patients may benefit from treatment with cyclosporine or cyclophosphamide.

FSGS can be idiopathic or secondary to glomerular hyperfiltration (including disorders with a reduced renal mass), viral infections or drug toxicity. Secondary forms usually present with nonnephrotic proteinuria, and primary forms with nephrotic syndrome. Several genetic abnormalities involving proteins of the glomerular epithelial cell cytoskeleton and cell junction proteins have been described in patients with familial NS; in some others, a factor increasing glomerular permeability has been identified (1, 2).

There has been a long debate as to whether Minimal Change Disease and FSGS are part of the same disease spectrum. Some patients with biopsy-proven minimal change disease later progress to FGS: in both, the response to corticosteroids is the major prognostic factor for progression to renal insufficiency and the same genetic defects have been described in both entities (3).

Epidemiology

In the past 20 years, the incidence of FSGS has increased considerably. It is the most common cause of NS, accounting for 35% of cases (33% for membranous nephropathy) in the general population, for more than 50% of cases in black adults and for 67% of such cases in black adults younger than 45 years of age. There has been an eleven-fold increase (United States Renal Data) of it as a cause of ESRD during a 20-year period (1980–2000) and it is now the most common cause of ESRD owing to primary glomerular disease in both black and white populations. In contrast, in other countries, the incidence of FSGS has not varied in the past years as shown by data from Europe.

The peak decade of life for ESRD incidence is 40 to 49 years in black subjects and 70–79 years in white individuals. Men have 1.5- to 2-fold greater risk than women (4, 5, 6).

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Pathogenesis

The podocyte constitutes a major portion of the glomerular filtration barrier that separates blood from the urinary space and has a pivotal role not only in genetic but also in many acquired forms of FSGS. The podocyte dysfunction may be caused by a primary T-cell disorder leading to the presence of circulating toxin (perhaps cytokines) or a genetic disease with mutations in genes that encode proteins which are localized to the slit diaphragms or which interact with the actin cytoskeleton. These proteins are vital for an intact glomerular barrier.

One gene located on chromosome 19q13 has been linked with familial autosomal dominant FSGS. It codes for nephrin, a major component of the slit diaphragm of the podocytes. NPHS2, a gene that codes for the protein podocin localized to the slit-diaphragm, is responsible of some recessive and sporadic forms (20–30% of steroid-resistant forms). It has been mapped to chromosome 1q25–31. The patients are heterozygotes for mutations in NPHS2 and compound heterozygotes for a nonconservative R229Q amino acid substitution in the same gene. Mutations that codes for other proteins, such as α-actin-4, CD2AP, and TRPC6 have also been identified in some cases of autosomal dominant forms of the disease. These forms present later and progress more slowly than recessive forms (7, 8) Table 91.1.

In others cases, a "circulating factor" of T-cell origin that is able to alter glomerular permeability has been hypothesized. This idea derives from the following observations: the frequent and immediate recurrence of proteinuria after renal transplantation in 30–40% of the corticosteroid-resistant cases, the beneficial effect of plasmapheresis or protein A immunoabsorption in these cases, and the transmission from mother with FSGS to fetus of the increase of the glomerular permeability. However, the identity of that plasma factor has not yet been discovered (9).

When a circulating factor is present, steroids and/or immunosuppressive agents may have a beneficial effect and recurrence after renal transplantation is frequent. The inherited forms do not respond convincingly to cyclophosphamide or cyclosporin A (CsA) and the disease does not recur after transplantation.

However, the difference between the genetic forms and those due to a circulating factor is not so clear and it has been hypothesized that idiopathic NS may be a multifactorial disease, including both pathogenic mechanisms, because in some patients with NPHS2, immunosuppressive drugs have a beneficial effect and in some others FSGS recurs after renal transplantation (10).

In addition to idiopathic forms, FSGS can be observed in a variety of secondary settings. In these cases, the histological injury results from an adaptive response to glomerular hypertrophy or hyperfiltration or from scarring of previous injury. This adaptative response occurs in diseases with nephron loss or renal vasodilatation (1).

Clinical Presentation

Most patients (60–75%) present with acute onset of the nephrotic syndrome. In addition, hypertension (45–65%) and microscopic hematuria (30–50%) are also commonly seen. The level of kidney function may vary (renal insufficiency in 25–50% of the cases). Slowly increasing, often nonnephrotic proteinuria and renal insufficiency over time are characteristic of the secondary disorders (1, 2) Table 91.2.

Histological Variants

The typical lesion of FSGS is a segmental solidification of the glomerular tuft owing to obliteration of the glomerular capillary lumen by a relative acellular matrix material on light microscopy and a diffuse epithelial foot process fusion on electron microscopy. The glomeruli not involved in the sclerotic lesion and the remaining part of the tuft of the glomeruli involved in the segmental lesion appear normal. Immunofluorescence microscopy only reveals nonspecific binding of IgM and complement (C3 and variably C1) in sclerotic lesions and very weak mesangial deposition of IgM.

Recently, five histopathological variants have been included in the diagnosis of primary FSGS (11) Figure 91.1:

1. classic FSGS or "NOS" (not otherwise specified) with the above-described typical histological lesion,
2. perihilar variant: Sclerosis and hyalinosis are perihilar. This variant is frequently observed in the secondary forms.
3. cellular variant: characterized by segmental hypercellularity in some glomeruli and "classic" lesions in others.
4. tip variant: the lesion occurs at the "tip" of the glomerulus near the beginning of the proximal tubule. This variant presents with a high incidence of NS and absence of chronic tubulointerstitial injury. It could include two conditions, one an early form of classic FSGS, and the other closely related to MCN.
5. collapsing variant: the entire glomerular tuft is collapsed and sclerosed. This variant may be primary or due to HIV infection, presents with NS, is often resistant to therapy and has the worst outcome of all the histological variants.

However, there is no significant difference in the response to steroid treatment among the patients with these different histopathological subsets (12), and it does not seem

that this new classification will help in selecting treatment protocols.

Natural History

Rates of remission of proteinuria and progression to ESRD were reported in a recent systematic review where data from 380 adult patients with FSGS and NS were analyzed (13). Two hundred and four (54%) patients were treated with steroids and different immunosuppressive drugs, and 138 (46%) were untreated. Fifty-five percent of treated patients ($n = 113$) achieved partial (22%) or complete remission (33%), only 20% ($n = 28$) achieved partial (17%) or complete remission (3%) ($p < 0.001$). The overall renal survival varies from 58 to 85.2% at 5 years and from 25 to 58% at 10 years. In patients without NS, the 10-year renal survival varies from 83 to 92% (14, 15).

Patients with FSGS are initially treated with corticosteroids and, irrespective of histological variant, steroid responsiveness is the best predictor of outcome in nephrotic patients. Failure to obtain remission is associated with a 50–60% likelihood of ESRD and complete remission is associated with no risk (12).

More recently, it has been demonstrated that even partial remission improves long-term renal survival (16).

Others predictors of outcome are nephrotic-range proteinuria and presence of interstitial fibrosis on biopsy. FSGS is more frequent and more severe in black and Hispanic men, both in adults and in children (12).

Relapse on Transplanted Kidney

Primary FSGS may recur in the renal allograft with a rate that varies from 30 to 56%. Recurrence is of rapid onset (during the first month in 66% of the cases) and results in a high rate of graft loss (13).

There is no difference in the frequency of recurrence between living, related or cadaveric transplants.

The inherited forms have very low recurrence rates (10% in the case with podocin mutations).

Reported risk factors for recurrence include age at onset of proteinuria (less than 20 years), recurrence in a prior allograft (the rate of recurrence is 80%), rapid deterioration from initial diagnosis to end-stage renal disease and mesangial hypercellularity in the native kidney (17).

Because of the risk of graft loss in recurrent disease, aggressive therapy including plasmapheresis or immunoadsorption is recommended. This approach improves graft survival (13).

Treatment

Clinically, it is important to distinguish secondary from primary FGS, because the treatment is different.

There have been no randomized clinical trials of steroid therapy in primary FSGS. In two systematic reviews, it was concluded that treatment with prednisone should be considered for patients with FSGS and NS (13, 18). Full dose (1 mg/kg/day with a maximum dose 50 to 80 mg/day) is

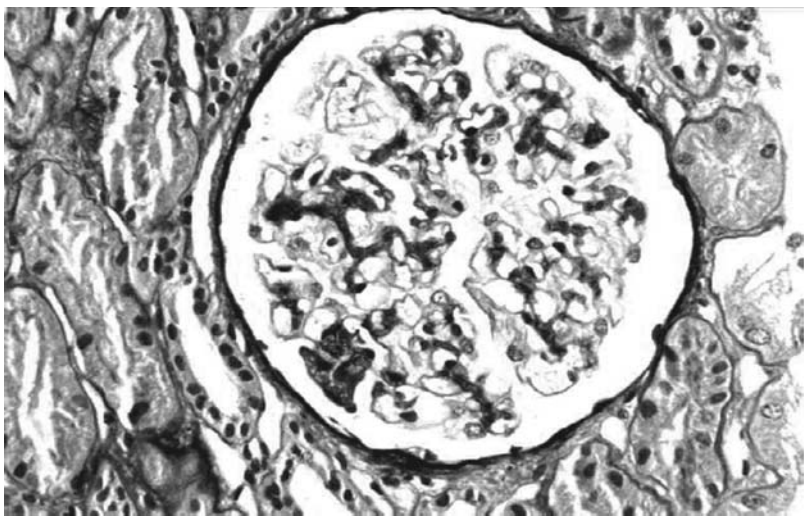

FIGURE 91.1. Focal and segmental Glomerulosclerosis (FSGS): Glomerular segmental sclerosis and collapsed with presence of hyaline. Silver Staining.

TABLE 91.1. Hereditary forms of FSGS.

Primary
Secondary
Hyperfiltration/reduced nephron mass
Reflux interstitial nephropathy
Morbid obesity
Solitary kidney
Glomerulopathies
Toxic agents
Heroin
Pamidronate
Viral infections
HIV-associated nephropathy
ParvovirusB19
Cytomegalovirus
Hereditary forms

given for 12–16 weeks followed, in case of even partial remission, by a slow tapering schedule over months (6–8 months) to avoid a rebound effect**.** The treatment must be sufficiently long (4 months at 1 mg/kg/day) before declaring the patient steroid resistant (1). The efficacy of steroids in patients with decreased kidney function is unclear and they are not indicated in case of nonnephrotic proteinuria. Only 50% of the patients achieve a complete remission of the proteinuria with such a protocol, 25% a partial remission, and 25% do not respond.

Cyclophosphamide and chlorambucil have been used since the 1950s and the best results are obtained in the cases with steroid dependency. Steroid resistance is highly predictive of resistance to alkylating agents (13).

Randomized controlled trials and uncontrolled studies have demonstrated the effectiveness of cyclosporine in reducing proteinuria in steroid-dependent and steroid-resistant FGS. The initial dose is approximately 5 mg/kg/day adjusted to 12-h levels of 100–150 ng/mL. CsA is discontinued at 3 months if there is no response. CsA dependency is observed but the likelihood of relapse appears to be lower if the cyclosporine treatment is prolonged up to one year or longer after remission is induced, and then gradually tapered and discontinued (13, 18).

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce proteinuria but remission is rarely attained. In addition, it is well known that they slow the rate of progression to ESRF. They are recommended in all patients with FSGS (19, 20).

TABLE 91.2. Classification of FSGS.

Gene	Protein	Disease	Inheritance
NPHS1	Nephrin	Congenital NS Finísh type	Autosomal recessive
NPHS2	Podocin	Steroid resistant NS	Autosomal recessive
CD2AP	CD2AP	Proteinuria in adolescence and early adulthood, chronic renal failure	Autosomal dominant
ACTN4	alpha-actin 4	Proteinuria in adolescence and early adulthood, chronic renal failure	Autosomal dominant

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