

Idiopathic focal segmental glomerulosclerosis: a favourable prognosis in untreated patients?

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ABSTRACT

Background: Patients with focal segmental glomerulosclerosis (FSGS) are considered to have a poor prognosis and spontaneous remissions are seldom reported. However, FSGS is not a single disease entity. Our aim was to describe the clinical course in initially untreated patients with recently diagnosed idiopathic FSGS.

Methods: This was a retrospective study of patients with a diagnosis of FSGS by histology, who fulfilled the following criteria: proteinuria >3.5 g/day, normal renal function, duration of proteinuria or hypertension of less than one year, normal-sized kidneys, no underlying renal disease, and a negative family history. Renal biopsies were reviewed without knowledge of the clinical course.

Results: Twenty patients (13 male, 7 female) fulfilled the study criteria. Median age was 49.3 (range 21.8 to 73.0) years, serum creatinine 90 ± 20 $\mu\text{mol/l}$, proteinuria 10.0 ± 5.5 g/day and serum albumin 24 ± 6 g/l. After a median follow-up of 9.4 (2.1-18.6) years, 13 patients (65%) were in remission of proteinuria. Renal function deterioration occurred in seven patients, and prompted treatment in four of them. The ten-year death-censored renal survival was 89%. Renal function deterioration and remission rate could be predicted by selectivity index, serum albumin at three months after renal biopsy and the percentage of glomeruli with segmental sclerosis.

Conclusion: Focal glomerulosclerosis is not a single disease. Case definition using strict clinical criteria identifies a subgroup of patients with idiopathic FSGS who have a good prognosis. In the majority of these patients immunosuppressive therapy is not warranted.

KEYWORDS

Idiopathic focal segmental glomerulosclerosis, immunosuppression, remission, renal survival, steroid treatment

INTRODUCTION

In recent years focal segmental glomerulosclerosis (FSGS) has become an increasingly important cause of the nephrotic syndrome in adults.^{1,2} In general, prognosis is considered to be poor in patients with FSGS and a nephrotic syndrome with up to 50% of patients proceeding to end-stage renal disease (ESRD) within five years.^{3,4} Spontaneous remissions are reported to be rare, occurring in less than 6% of untreated patients.^{4,7} Retrospective studies have suggested that complete remissions may develop in up to 60% of patients after prolonged treatment with immunosuppressive drugs.^{6,8} Therefore, a trial of steroid therapy is recommended in all nephrotic patients with primary FSGS.³ Attainment of a complete remission heralds a favourable prognosis with less than 15% of such patients developing ESRD. However, the literature data on prognosis and outcome of patients with FSGS must be interpreted with caution since FSGS is a descriptive, histological diagnosis and not a single disease entity.^{9,10} Secondary forms of FSGS occur frequently, and may result from nephron loss (hypoplastic kidney, reflux nephropathy), other underlying renal diseases, longstanding hypertension, or obesity. If no underlying causes are identified, FSGS is classified as primary, idiopathic FSGS. In recent years it has become evident that in some of these patients the

disease may be caused by mutations in podocyte proteins such as α -actinin-4 and podocin.^{11,12}

Discrepancies between studies may thus be explained by differences in the distribution of the various types of FSGS in the studied populations. For example, in a recent study that described the natural history of patients with FSGS, the mean serum albumin of the patients was 37 g/l, which strongly suggests that patients with secondary forms of FSGS were included.¹³

We retrospectively studied the outcome in a subgroup of patients with idiopathic FSGS. To avoid bias caused by including patients with other types of FSGS as far as possible, we applied a set of strictly defined clinical exclusion criteria. Because it was our policy to withhold immunosuppressive treatment in the majority of patients with FSGS without renal function deterioration, we were able to determine the outcome of FSGS in a cohort of untreated patients.

MATERIALS AND METHODS

We identified all patients diagnosed with FSGS between 1980 and 1996 from the pathology registry at the Radboud University Nijmegen Medical Centre and affiliated hospitals. Since the aim of this study was to assess the clinical course in adult patients with recent-onset idiopathic FSGS, we included adult patients (≥ 18 years at biopsy) with a proteinuria ≥ 3.5 g/day and a serum creatinine ≤ 135 $\mu\text{mol/l}$ in the study. To avoid bias by including patients with hereditary or secondary forms of FSGS or patients with longstanding disease, the following exclusion criteria were used: evidence of hypoplastic kidney, renal agenesis, prior nephrectomy, underlying renal disease, obesity (BMI > 32 kg/m²), longstanding proteinuria (> 12 months) or hypertension (> 12 months), family history of renal disease, underlying malignancy, intravenous drug abuse, evidence of human immunodeficiency virus (HIV) infection or renal insufficiency (serum creatinine > 135 $\mu\text{mol/l}$). During the study period most nephrologists in the participating hospitals considered FSGS to be prednisone resistant, based on the available data that short-term prednisone therapy was mostly unsuccessful. More intensive immunosuppressive therapy was used in patients with evidence of renal function deterioration (increase in serum creatinine $> 50\%$).

All renal biopsies of the patients who were included in our study were reviewed by two renal pathologists (KA and ES), who were unaware of patient outcome. A diagnosis of FSGS was made using the criteria recently described by D'Agati *et al.*¹⁴ Based on these criteria we discerned five light microscopic patterns of FSGS: FSGS not otherwise specified (NOS), perihilar variant, cellular variant, tip variant and collapsing variant.

For quantitative analysis all available glomerular cross-sections were numbered. Twenty-five glomerular profiles were selected at random by one of us and these profiles were evaluated by the renal pathologist (KA) for the presence of sclerosis, synechia, hyalinosis, collapse of the glomerular tuft, podocyte hypertrophy and foam cells.

DEFINITIONS

End-stage renal disease (ESRD) was defined as a serum creatinine of > 450 $\mu\text{mol/l}$ or the need for renal replacement therapy. Nephrotic syndrome was defined as a proteinuria of > 3 g/day together with a serum albumin of < 30 g/l and massive proteinuria was defined as proteinuria > 10 g/day. Patients with a systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg were considered hypertensive. A complete remission was defined as proteinuria < 0.2 g/day with a stable serum creatinine < 135 $\mu\text{mol/l}$ and a partial remission was defined as proteinuria between 0.2 g/day and 2.0 g/day with a stable serum creatinine < 135 $\mu\text{mol/l}$. A relapse was defined as a proteinuria > 3.0 g/day after prior reduction of the proteinuria to less than 2.0 g/day. Protein selectivity index was calculated as the clearance of IgG divided by the clearance of transferrin.¹⁵ Proteinuria was considered selective if the selectivity index was below 0.2.

STATISTICAL ANALYSIS

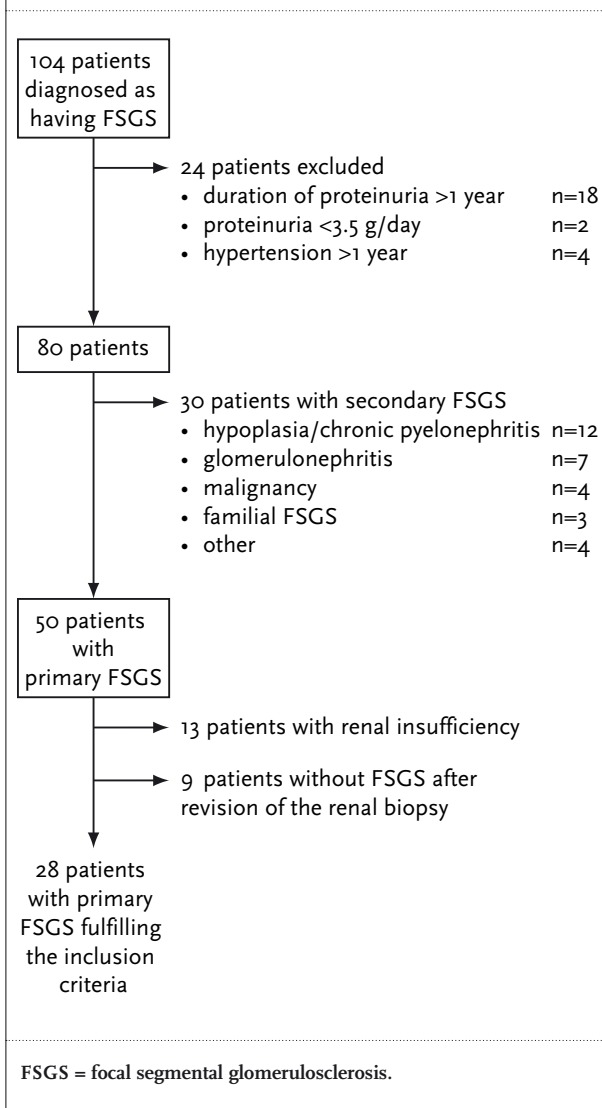
Values are given as means \pm SD or median (range) when appropriate. For comparison between groups, unpaired T-test or Mann-Whitney U test were used for continuous data and Fisher's exact test was used for categorical data. Cumulative renal survival and cumulative remission rates were calculated with Kaplan-Meier survival curves. A p value of 0.05 was considered to be the level of statistical significance.

RESULTS

In the period 1980 to 1996 a diagnosis of FSGS was made in 104 patients. Based on strict clinical criteria, 37 of these 104 patients were considered to have recent-onset idiopathic FSGS (*figure 1*).

On revision of the renal biopsies a diagnosis of FSGS was confirmed in 28 patients. FSGS lesions were not present in the biopsies of nine patients. The renal biopsies of these patients showed early lesions consisting of hyalinosis and/or foam cells and/or collapse of the glomerular tuft and/or glomerular epithelial cell hypertrophy and/or mesangial hypercellularity.

Figure 1 Flow chart of selection of patients with idiopathic focal glomerulosclerosis



Twenty patients were initially not treated, and they form the basis of this study. Thirteen out of these 20 patients received an angiotensin-converting enzyme inhibitor (ACEi), which was standard therapy for patients with proteinuria after 1988. Patient characteristics at biopsy of the 20 patients are presented in table 1. For comparison we have also provided the characteristics of the patients (n=8) who were treated with prednisone within a few months after the renal biopsy. Twenty-seven patients were Caucasian and one patient was Indonesian. A nephrotic syndrome was present in all patients, except for one patient who had a serum albumin of 43 g/l at biopsy. Proteinuria >10 g/day was present in ten patients. The findings on renal biopsy are presented in table 2. Most patients were classified as tip variant; only three patients had FSGS-NOS. All patients studied had evidence of diffuse foot process effacement.

Table 1 Patient characteristics at biopsy

	Initially untreated (n=20)	Treated (n=8)
Sex (male/female)	13/7	5/3
Age at biopsy (years)	49.3 (21.8-73.0)	42.4 (19.5-67.4)
Serum albumin (g/l)	24 ± 6	18 ± 5*
Serum creatinine (μmol/l)	90 ± 20	81 ± 17
Creatinine clearance (ml/min; n=22)	101 ± 34	123 ± 35
Serum cholesterol (mmol/l; n=23)	11.3 ± 2.3	11.6 ± 2.9
Proteinuria (g/day)	10.0 ± 5.5	9.8 ± 3.1
Proteinuria >10 g/day (n)	7 (35%)	3 (38%)
Selectivity index (n=23)	0.21 ± 0.09	0.15 ± 0.05
Hypertension (n)	16 (80%)	4 (50%)
Systolic blood pressure (mmHg)	155 ± 16	146 ± 13
Diastolic blood pressure (mmHg)	91 ± 9	82 ± 8*
Interval presentation biopsy (months)	2.1 (0.7-10.6)	4.5 (0.7-7.6)
Follow-up (years)	9.4 (2.1-18.6)	9.2 (4.0-11.2)

Values are given as means (± SD) or median (range).
*P < 0.05 for comparison between treated and untreated patients.

Outcome of untreated patients

As mentioned above, 20 patients were initially left untreated. Fourteen of these 20 patients developed a spontaneous partial remission. The nephrotic syndrome persisted in six patients. Time between biopsy and partial remission varied between 1.4 and 36.7 months, with a median of 9.9 months. Cumulative incidence of partial remission at one, three and five years after biopsy was 40, 73 and 73% respectively. Two patients with a partial response have relapsed, one patient had a sustained partial remission, whereas 11 patients developed a persistent complete remission of proteinuria. Serum creatinine increased more than 50% in all six patients with a persistent nephrotic syndrome and in one patient who relapsed after a partial remission. Four of these seven patients were treated with immunosuppressive drugs, either prednisone monotherapy (n=1) or prednisone combined with cyclophosphamide (n=3). Patients received prednisone at a dose ≥60 mg/day for an average of 2.5 ± 0.9 months; thereafter the prednisone dose was progressively tapered. Cyclophosphamide was given in a dose of 150 mg/day for three months. Treatment resulted in a partial remission in one patient, and nephrotic range proteinuria persisted in two patients; however, renal function improved in both patients and remained stable until the end of follow-up,

Table 2 Findings in renal biopsies of treated and untreated patients

	Initially untreated (n=20)	Treated (n=8)
Number of glomeruli per biopsy	26 (4-87)	13 (4-62)
<i>Light microscopy (n=24)</i>		
NOS variant (n)	3	2
Tip variant (n)	13	6
Collapsing variant (n)	2	0
Perihilar variant (n)	2	0
<i>Fluorescence microscopy (n=26)*</i>		
Segmental IgM and/or C3 depositions (n)	17	6
Patients without depositions (n)	2	1

N = number of patients; NOS = not otherwise specified.
*Fluorescence microscopy was not available in two patients.

and one patient progressed to ESRD. In the three patients with declining renal function who did not receive immunosuppressive drugs, one patient progressed to ESRD, one patient had persistent nephrotic proteinuria and one patient had persistent non-nephrotic proteinuria. Renal function deteriorated progressively in both patients with persistent proteinuria. Treatment with an ACEi was not different between patients who achieved a complete remission (7 out of 11) and patients with deterioration in renal function (4 out of 7). Clinical status at the end of follow-up is given in table 3. One patient (5%) with persistent proteinuria died due to a myocardial infarction, 2.3 years after diagnosis. Renal survival was 100, 84 and 84% at one, five and ten years after biopsy, respectively. Renal survival censored for death at one, five and ten years after biopsy was 100, 89 and 89%. For comparison, clinical status at the end of follow-up is also presented for the treated patients (table 3)

In this group of initially untreated patients we tried to define the characteristics that would allow us to predict prognosis. The following parameters were evaluated: serum albumin, proteinuria and protein selectivity index (all measured at the time of biopsy), serum albumin, proteinuria and a combination of increased levels of proteinuria or decreased concentrations of serum albumin (all measured at three months after biopsy), histological variants of FSGS and the percentage of glomerular profiles with sclerosis, synechia or hyalinosis on renal biopsy. A higher percentage (>25%) of sclerosis in the glomeruli, nonselective proteinuria at the time of biopsy and decreased concentrations of serum albumin at three months after renal biopsy were associated with a higher rate of renal failure (table 4).

Table 3 Clinical status at the end of follow-up in treated and untreated patients

	Initially untreated (n=20)	Treated (n=8)
Complete remission	11 (55%)	1 (12.5%)
Partial remission	2 (10%)	1 (12.5%)
Persistent proteinuria	4 (20%)	2 (25%)
ESRD	2 (10%)	1 (12.5%)
Deceased	1 (5%)	3 (37.5%)

ESRD = end-stage renal disease.

Table 4 Predictors of deterioration of renal function in initially untreated patients

	Deterioration of renal function*		P value†
	Yes (n=7)	No (n=13)	
<i>Selectivity index‡</i>			<0.01
≤0.2	0	8	
>0.2	7	2	
<i>Serum albumin at three months</i>			<0.01
<20 g/l	4	0	
≥20 g/l	3	13	
<i>Sclerosis</i>			<0.01
<25% of glomerular profiles	2	13	
≥25% of glomerular profiles	5	0	

*Deterioration of renal function was defined as an increase in serum creatinine of >50%. †P values were calculated by Fisher's exact test.
‡The selectivity index patients was not available in three patients.

DISCUSSION

We aimed to study the outcome in a well-defined subgroup of patients with a nephrotic syndrome due to idiopathic FSGS. Therefore, we selected patients with FSGS who fulfilled strict criteria i.e. normal-sized kidneys, absence of underlying glomerular disorders, negative family history of renal disease, no longstanding proteinuria or hypertension, no morbid obesity and normal renal function. We observed that more than half of the untreated patients showed a spontaneous partial or complete remission of proteinuria, clearly different from previous studies in patients with FSGS that report spontaneous remission rates of 6 to 7%.^{4-6,16} We feel that our study underlines that FSGS is not a single disease entity, but rather a common phenotypic expression (on histology) of various

diseases that differ in pathogenesis, prognosis and response to therapy.¹⁰ This is supported by the fact that literature data on the prognosis and outcome of treatment in patients with FSGS are quite diverse. In contrast to our study, many studies that report low remission rates have included patients with decreased renal function at presentation or at the time of renal biopsy,^{4,6,17} patients with non-nephrotic proteinuria,¹⁶ patients with longstanding proteinuria^{16,18} and patients with normal serum albumin.¹³ Furthermore, many studies do not mention the specific criteria that were used to select patients.

In recent years it has become evident that FSGS can result from mutations in podocytic proteins such as nephrin, α -actinin-4 and podocin.^{11,12} Mutations may not only be present in patients with familial forms of FSGS but also in some patients with sporadic forms of FSGS.^{19,20} In our patients DNA typing was not performed. However, because of our exclusion criteria (family history of renal disease, age <18 years, longstanding proteinuria) it is unlikely that patients with mutations were included. Although our study is retrospective in nature, we tried to avoid potential bias as far as possible. First, we have included all patients derived from the pathology registry. In addition, the composition of the study population was based on predefined clinical criteria without knowledge of the outcome. Finally, all renal biopsies were revised and only patients with typical lesions of FSGS were included. In the period between 1980 and 1996 not all physicians adhered to the same treatment strategy. Thus eight patients were initially treated. Nevertheless, if untreated and treated patients are grouped together, still 12 out of 28 patients with a normal renal function have a persistent spontaneous remission of proteinuria.

Four of the initially untreated patients received immunosuppressive therapy after deterioration of the renal function. In some of these patients treatment was successful, and renal function improved in three out of four patients. Results might have been even better if we had used immunosuppressive therapy for a longer period of time, as has been suggested by recent studies.^{4,8,21}

If spontaneous remissions occur frequently, it is important to be able to predict outcome at an early stage to allow tailor-made treatment. In our patients, nonselective proteinuria, a higher percentage of sclerotic lesions on renal biopsy and low levels of serum albumin at three months after renal biopsy predicted prognosis. Because of the small number of patients in our study we could not define the most predictive variable.

Recent studies suggest that the occurrence of the 'tip lesion' variant of FSGS identifies a group of patients with a better prognosis.^{22,23} Due to the small number of patients with FSGS variants other than the tip lesion we were unable to determine whether the histological variant of FSGS can predict the occurrence of a spontaneous

remission. However, in agreement with our findings, these studies have also demonstrated that a higher percentage of sclerotic lesions predicts a worse prognosis.^{22,23} In a recent study Bazzi *et al.* concluded that the fractional excretion of IgG (FE IgG) predicted prognosis in patients with FSGS.¹⁵ These authors measured FE IgG in 29 patients with FSGS and normal renal function of whom 27 were treated. FE IgG could predict remission in 91% and progression to ESRD in 71% of patients, respectively. This confirms our findings that qualitative markers of proteinuria such as FE IgG and selectivity index are important predictive variables.

In conclusion, clinical criteria allow us to identify a group of patients with recent-onset idiopathic FSGS that have a favourable prognosis. Many of these patients will develop a spontaneous remission of proteinuria. In these patients immunosuppressive therapy is not warranted unless renal function deteriorates. Future studies should allow identification of laboratory parameters and histological criteria that predict outcome with high sensitivity and specificity.

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