

Clinicopathological correlation and treatment response of primary focal segmental glomerulosclerosis in adults and adolescents

J. Dhanapriya, T. Dineshkumar, N. Gopalakrishnan, R. Sakthirajan, T. Balasubramaniyan

Department of Nephrology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India

ABSTRACT

The incidence of focal segmental glomerulosclerosis (FSGS) is approximately 10% in children <6 years, 20% in adolescents, and 20–25% in adults. A retrospective observational study was done to document clinicopathological correlation, treatment response, and risk factors in the progression of chronic kidney disease (CKD) of primary FSGS in adults and adolescents. A total of 170 patients were studied with a mean follow-up of 4.32 ± 1.2 years. FSGS not otherwise specified was the most common subtype (56%) followed by tip variant (24%). About 32% had complete remission (CR) at a mean time of 6.4 months, 23% had partial remission (PR) at a mean time of 5.7 months, and 45% had no response to steroids. Persistent nephrotic proteinuria at 3rd and 6th month and presence of interstitial fibrosis and tubular atrophy >30% in renal biopsy are the independent predictors of poor response to treatment. Presence of anemia, interstitial fibrosis, and tubular atrophy of >30% in renal biopsy and the absence of remission after treatment were the independent predictors of CKD progression. Overall renal survival was 78% at 3 years and 54% at 5 years. Renal survival difference with or without nephrotic proteinuria at onset was 39% and 69% at 5 years. Renal survival was higher in patients with normal renal function (66%) compared with those who had renal failure (42%) at 5 years. Renal survival at 5 years for CR was 69%, PR was 49%, and no remission was 42%.

Key words: Chronic kidney disease, primary focal segmental glomerulosclerosis, remission, risk factors, steroids

Introduction

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome, accounting for 20–25% of nephrotic syndrome in adults.^[1] Around 50% of patients reach end-stage renal disease (ESRD) at 8 years, accounting for 20% of dialysis patients. Kitiyakara *et al.* reported an 11-fold increase in FSGS among dialysis patients older than 21 years.^[2] Remission rates of 80% can be achieved with longer treatment,

and is an independent predictor of renal survival.^[3] In adults, responsiveness to steroids usually takes up to 16 weeks, and can be slowly tapered over 3–6 months. Our aim was to study the epidemiological profile and clinicopathologic correlation of primary FSGS in adults and adolescents. Treatment response and risk factors in the progression of chronic kidney disease (CKD) was also studied.

Subjects and Methods

This was a retrospective observational study in adult and adolescent patients (age 13–60 years) with biopsy proven FSGS during the period of January 2007 to December

Address for correspondence:

Dr. J. Dhanapriya,
Department of Nephrology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai - 600 003, Tamil Nadu, India.
E-mail: priyamdhana@yahoo.co.in

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2013. All patients treated with oral prednisolone for 24 weeks with at least 6 months follow-up were included. We excluded patients with secondary FSGS, patients who did not receive steroid therapy, poor compliance with drugs, and follow-up with <6 months.

Demographic profile, clinical examination, laboratory parameters viz urine analysis, 24 h urine protein, serum creatinine, blood urea, serum albumin, and lipid profile at the onset of disease and renal biopsy details were analyzed. The diagnosis of FSGS was made when at least one glomerulus shows a typical sclerotic lesion in a segment in light microscopy. Subtyping of FSGS was performed in according to Columbia classification described by D'Agati.^[4] All patients were started on oral prednisolone 1 mg/kg/day and continued for 6 months, tapered and stopped within 1-month. If there was no response to steroids at 6 months, they were started on second-line drugs that include oral cyclophosphamide, cyclosporine A (CSA), tacrolimus, or mycophenolate mofetil (MMF). All received a maximal tolerable dose of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers along with supportive treatment and statins.

Definitions

- Complete remission (CR) – proteinuria <0.3 g/day with a stable serum creatinine (<50% increase from baseline)
- Partial remission (PR) – proteinuria between 0.3 and 3.5 g/day with at least 50% reduction in proteinuria from the baseline and a stable serum creatinine
- Relapse – proteinuria >3.5 g/24 hr after remission
- CKD – CrCl <60 ml/min/1.73 m² after 3 months
- ESRD – CrCl <15 ml/min/1.73 m² or the need for dialysis or renal transplantation.^[1,5]

Statistical analysis

All variables were expressed in mean \pm standard deviation or percentage. Univariate analysis was done by Fisher's exact test and Chi-square test for categorical variables and analysis of variance was used for continuous variables. Statistical significant variables by univariate analysis were subjected to linear regression analysis to assess multivariable association. Renal survival rate was determined by the Kaplan–Meier method. The log-rank test was used to evaluate the significance of the difference between survival mean values in subgroups. Statistical analysis was done with SPSS software 16 (SPSS Inc., Chicago, IL). In all analytic procedures, $P < 0.05$ was considered as significant. Institutional Ethics Committee approval was obtained.

Results

A total of 170 patients were included with a mean follow-up of 4.32 ± 1.2 years. About 65% were males (male: female ratio – 1.9:1). The predominant age group was between 21 and 40 years accounting for 54% of total patients. Baseline patient characteristics at the time of biopsy are shown in Table 1. The most common symptom was edema (98%), followed by nephrotic proteinuria (79%), hypertension (41%), microhematuria (30%), sub-nephrotic proteinuria (21%), and renal failure (20%). Venous thrombosis and cellulitis due to anasarca were occurred as complications of disease process. Infection is the most common complication followed by cushingoid features due to drugs. Two patients suffered from glaucoma and eight patients had cataract due to steroid therapy.

Response to treatment as defined previously is expressed as CR, PR, and NR, and the details of immunosuppression therapy are described in Table 2. About 49% of the patients progressed to CKD at mean follow-up. Incidence of ESRD is 17% at a mean time of 4.32 years and two patients died due to uremia at a mean time of 2.4 years. During follow-up, 13 patients out of 93 who achieved remission (CR or PR) had a relapse at a mean duration of 2.8 years. Eighty percentage of them had prior PR only.

Not otherwise specified (NOS) was the most common lesion, present in 96 (56%), followed by tip variant in 41 (24%), perihilar type in 16 (10%), and cellular

Table 1: Baseline characteristics of patients with primary FSGS

Variables	Mean \pm SD	Range
Age (years)	29.2 \pm 13.1	13-60
Systolic blood pressure (mmHg)	132 \pm 45	90-220
Diastolic blood pressure (mmHg)	84 \pm 23	60-120
BMI	24.7 \pm 13	20-29
Proteinuria (g/day)	4.26 \pm 1.9	1.5-9
Serum creatinine (mg/dl)	1.24 \pm 0.56	0.6-5
Creatinine clearance (ml/min)	85.8 \pm 34	30-140
Hemoglobin (g/dl)	11.6 \pm 4.5	7-15
Serum cholesterol (mg/dl)	215 \pm 111	118-540
Serum albumin	3.4 \pm 0.7	2.5-4.2

FSGS: Focal segmental glomerulosclerosis, BMI: Body mass index, SD: Standard deviation

Table 2: Treatment response

Drug	Number	CR	PR	NR
Prednisolone (%)	170	54 (32)	39 (23)	77 (45)
Cyclophosphamide (%)	6	Nil	Nil	6 (100)
Cyclosporine	3	Nil	2	1
Tacrolimus	2	Nil	2	Nil
MMF	4	Nil	1	3

CR: Complete remission, PR: Partial remission, NR: No remission, MMF: Mycophenolate mofetil

15 (9%). Only two (1%) patients had collapsing FSGS and reached ESRD in 2.2 years. Mesangial hypercellularity and intra-glomerular foam cells were present in 11% and 26%, respectively. Significant interstitial fibrosis and tubular atrophy was present (>30% of cortical parenchyma) in 29% of patients. Hyaline arteriosclerosis was seen in 94 patients (55%). Around 90 patients (53%) showed IgM positivity and 56 patients (33%) had C3 positivity in immunofluorescence.

Among subtypes, perihilar variant was present with less microhematuria, nephrotic proteinuria compared to NOS ($P < 0.001$), and cellular variety ($P < 0.001$). Cellular variant was present more with renal failure ($P < 0.05$) at presentation versus tip variant and more arterial hyalinosis in renal biopsy ($P < 0.05$) compared to the perihilar lesion. Hypoalbuminemia ($P 0.001$) was commonly seen in tip lesion and hypertension in perihilar variant ($P = 0.007$) compared to other groups. Interstitial fibrosis and tubular atrophy were seen more in NOS ($P = 0.007$) versus cellular variant. CR was seen more in tip variant ($P 0.001$) when compared to others. Less remission and progression to CKD was increasingly noted in NOS type compared to tip lesion ($P = 0.003$ and $P = 0.009$, respectively).

Predictors of poor response to treatment and progression to CKD are given Table 3. Overall renal survival was 78% at 3 years and 54% at 5 years. Renal survival was significantly higher in patients presented with normal renal function compared with those with renal failure at presentation with 66% versus 42% at 5 years. Renal survival difference with or without nephrotic proteinuria at onset was 39% versus 69% at 5 years [Figure 1]. Renal survival by Kaplan–Meier analysis at 5 years with CR was 69%, PR was 49%, and NR was 42% [Figure 2]. There was no significant difference between those achieve PR and nil response.

Discussion

FSGS is characterized by marked proteinuria, variable steroid responsiveness hypertension, and a risk of progression to CKD.^[5] Classification of FSGS include primary, genetic, and secondary. Primary (idiopathic) occurs without known inciting injury.^[4] A working group has defined five subtypes of FSGS^[6] based on light microscopy (Columbia classification) which include collapsing FSGS, tip lesion, cellular, perihilar variant, and NOS.

The most common symptom was edema (98%), followed by nephrotic proteinuria (79%), hypertension (41%), and renal insufficiency (20%), while Singh *et al.*^[7] showed hypertension in 42.2%, gross hematuria in 36.4%, micro-hematuria in 63.6%, and azotemia in 37.5%. Mean proteinuria was 5.53 ± 2.89 g/day while in our study it was 4.26 ± 1.9 g/day. Taheri *et al.*^[8] reported mean systolic blood pressure of 121.19 mmHg, diastolic blood pressure of 77.52 mmHg, serum creatinine of 1.18 mg/dl, plasma albumin of 3.29 g/dl, and glomerular

Table 3: Predictors of poor treatment response and CKD progression (univariate analysis)

Variable	Poor response to treatment P value	CKD progression P value
Male sex	-	0.05
Nephrotic proteinuria at the onset	0.01	0.05
Persistent nephrotic at 3 months	<0.001*	0.001
Persistent nephrotic at 6 months	<0.001*	0.001
Renal failure at the onset	0.03	0.04
Persistent renal failure at 3 months	0.05	0.006
Persistent renal failure at 6 months	0.01	0.001
Anemia*	-	0.03*
Hypertension	-	0.03
Nil remission*	-	<0.001*
Interstitial fibrosis, tubular atrophy >30%*	0.007*	0.006*

*Statistical significance in multivariate analysis also. CKD: Chronic kidney disease

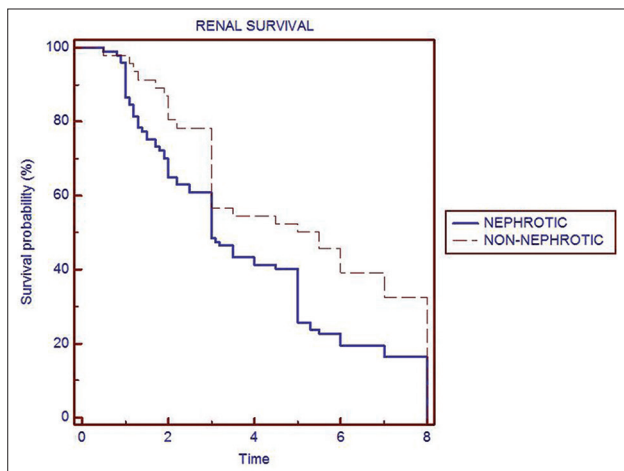


Figure 1: Renal survival at 5-year nephrotic versus nonnephrotic proteinuria

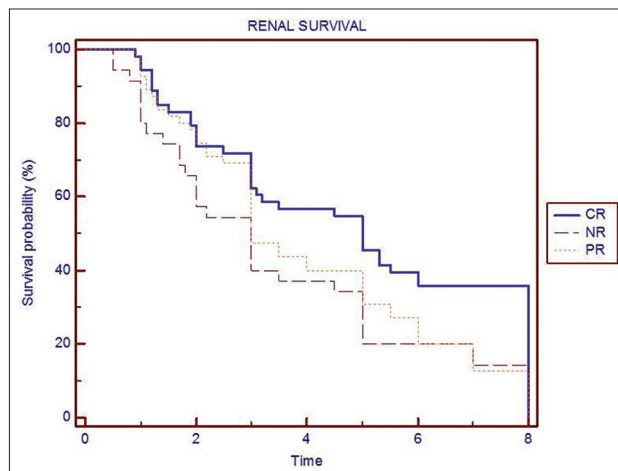


Figure 2: Survival analysis by Kaplan–Meier method

filtration rate of 87.18 ml/min, while in our study it was 132 mmHg, 84 mmHg, 1.24 mg/dl, 3.4 mg/dl, and 85.8 ml/min, respectively.

On steroid therapy, PR occurred earlier in those who eventually achieved CR. Hence, early partial response is the predictor of CR. Miyata *et al.*^[9] reviewed 32 FSGS patients with steroids alone in which 44% had CR, 12% had PR, and 44% had nil response. The prospective Regional Glomerulonephritis Registry Study^[10] followed 95 adult and pediatric patients with FSGS, for a mean period of 61 months and showed a remission rate of 39% in adults after prolonged therapy with steroids.

Relapse occurred in 14% cases at a mean time of 2.8 years who achieved remission. In other studies where relapse rate was reported as high as 40%. Males (80%) had more relapse than females. CSA is the only agent tested by randomized controlled trials in adults with FSGS.^[11] The main drawback of CSA is that 40–75% patients experience a relapse within 2 months of stopping or tapering the drug.^[12] In a recent study of 25 patients with steroid-resistant FSGS, who were treated with tacrolimus (0.15 mg/kg/day) and full dose prednisone for at least 8 weeks, CR was achieved in 40% and PR in 8%.^[13] Briggs *et al.*^[14] reported a remission rate of 66% with MMF in steroid resistant FSGS and is an alternative to CSA in patients with progressive renal failure due to its negligible side effects on renal hemodynamics and metabolic profile. Lanewala *et al.*^[15] showed steroid-dependent nephrotic syndrome in 63.8% and steroid resistance in 35% of children with idiopathic FSGS. They also showed that majority of them could achieve high rates of sustained remission with second- and third-line immunosuppressive drugs.

NOS was the most common subtype (56%), followed by tip variant (24%), perihilar (10%), cellular (9%), and collapsing (1%). In a study by Deegens *et al.*, tip lesion was the most common (37%), followed by NOS (32%), perihilar (26%), and collapsing (5%).^[16] Schwartz and Lewis^[17] showed IgM positivity in 17% and mesangial cellularity in 16%. Presence of mesangial hypercellularity and hyalinosis was suggested as predictors for lower remission rate.^[18] The tip variant was associated with highest remission rate in our study of 70% while other studies also showed higher remission rate of 57–60%. A study of primary FSGS in children <17 years from Pakistan showed NOS as the highly prevalent variant.^[19]

By multivariate analysis, persistent nephrotic proteinuria at 3rd and 6th month and presence of interstitial fibrosis and tubular atrophy >30% in renal biopsy were the

independent predictors of poor renal response to treatment. Risk factors such as male gender, nephrotic proteinuria at onset, persistent nephrotic proteinuria at 3 and 6 months, renal failure at onset, persistent renal failure at 3 and 6 months, presence of hypertension, anemia, interstitial fibrosis and tubular atrophy of >30% in renal biopsy, and NR after treatment predicted the progression to CKD at mean follow-up. Of this, last three factors were the independent predictors. Absence of remission was the single strongest predictor for the progression of CKD. Most studies demonstrated that presence of significant interstitial fibrosis was the only independent predictive factor for response to treatment.^[20,21] Korbet^[1] showed that serum creatinine >1.3 mg/dl, range of proteinuria, and interstitial fibrosis >20% were positive predictors of the occurrence of ESRD.

Overall renal survival by Kaplan–Meier survival analysis was 78% at 3 years and 54% at 5 years. Renal survival was significantly higher in patients presented with normal renal function (66%) compared with those with renal failure (42%) at 5 years. Renal survival difference with or without nephrotic proteinuria at onset was 39% versus 69% at 5 years. Renal survival at 5 years for CR was 69%, for PR 49%, and for NR 42%. There was no significant difference between those achieve PR and nil response. Therefore, attaining CR significantly improves renal survival. Renal survival rates were 68.6% and 27.3% at 5 and 10 years, respectively, in a study by Singh *et al.*^[7] Cameron^[22] reported 5-year and 10-year survival rates as 70% and 40%, respectively.

This study involves significant number of patients with longer duration of follow-up from India and validates the observation that nonremission of proteinuria is the strongest risk factor for CKD progression. The limitations include retrospective analysis and the role of immunosuppressants other than steroids was not studied due to less number.

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Conflicts of interest

There are no conflicts of interest.

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