

Clinical course of primary focal segmental glomerulosclerosis (FSGS) in Turkish children: a report from the Turkish Pediatric Nephrology FSGS Study Group

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SUMMARY: Beşbaş N, Özaltın F, Emre S, Anarat A, Alpay H, Bakkaloğlu A, Baskın E, Buyan N, Dönmez O, Düşünsel R, Ekim M, Gök F, Gür-Güven A, Kavukçu S, Mir S, Sönmez F. Clinical course of primary focal segmental glomerulosclerosis (FSGS) in Turkish children: a report from the Turkish Pediatric Nephrology FSGS Study Group. Turk J Pediatr 2010; 52: 255-261.

The clinical course of focal segmental glomerulosclerosis (FSGS) is heterogeneous in children. To evaluate the clinical course and the predictors of outcome in Turkish children with primary FSGS, a retrospective study was conducted by the Turkish Pediatric Nephrology Study Group in 14 pediatric nephrology centers. Two hundred twenty-two patients (92 boys, 130 girls, aged 1-16 years) with biopsy-proven primary FSGS were included. One hundred forty-eight patients were followed-up for a median of 51 months (range: 0.26-270). The clinical course was characterized by complete remission in 50 (33.8%), persistent proteinuria in 50 (33.8%) and progression to renal failure in 48 (32.4%) patients. Progression to end-stage renal disease (ESRD) was significantly higher in patients who did not attain remission. Complete remission, partial remission and progress to renal failure were recorded in 37%, 32% and 28%, respectively, of the patients (n=73) treated with prednisone combined cyclophosphamide/cyclosporine A. However, in patients (n=33) treated with pulse methyl prednisolone plus oral prednisone (up to 20 months) combined with cyclophosphamide, complete remission in 51.5% and partial remission in 27.3% of the patients were noted. Progression to renal failure was observed in 9.1% of this group of patients. Multivariate analysis showed that only plasma creatinine at presentation was an independent predictive value for outcome. Patients with serum creatinine level higher than 1.5 mg/dl had 6.6 times increased rate of progression to renal failure. Failure to achieve remission is a predictor of renal failure in children with primary FSGS. The use of immunosuppressive treatment in conjunction with prolonged steroid seems beneficial in primary FSGS in children.

Key words: children, focal segmental glomerulosclerosis, treatment outcome.

Focal segmental glomerulosclerosis (FSGS) is one of the most common diseases that progresses to end-stage renal disease (ESRD) in children. The long-term outcome in patients with FSGS is not satisfactory, and 20-30% of

patients may develop renal failure over a period of five years^{1,2}. The clinical course of primary FSGS varies, and there are controversies as to which factors are of importance in determining prognosis. Nephrotic range proteinuria and high serum creatinine levels at presentation

are considered risk factors for progression of FSGS and chronic renal failure^{3,4}. However, the poor prognosis associated with the nephrotic syndrome is significantly improved for those patients with a complete remission⁵. Recently, it has been shown that the best predictor of outcome in nephrotic patients with primary FSGS, irrespective of histologic variant, is a remission in proteinuria⁶. In this nationwide retrospective cohort study, we attempted to evaluate the clinical course and the predictors of outcome in Turkish children with primary FSGS.

Material and Methods

Patients

This retrospective study was conducted by the Turkish Pediatric Nephrology FSGS Study Group, in which 14 pediatric nephrology centers participated. Two hundred twenty-two children with primary FSGS aged 1-16 years at presentation were included. Inclusion criteria for patients were as follows: nephrotic syndrome (defined as proteinuria >40 mg/m²/h or urine protein (mg)/creatinine (mg) ratio >2 accompanied by serum albumin <2.5 g/dl and edema) or nephrotic range proteinuria (urine protein/creatinine ratio >2 or proteinuria >40 mg/m²/h) plus biopsy-proven primary FSGS. Presence of any known causes of secondary FSGS was a definite exclusion criterion. Clinical questionnaires that had been developed for this study were distributed to 14 pediatric nephrology centers. Data were collected and analyzed in the Turkish Pediatric Nephrology FSGS Study Group Data Coordinating Center of Hacettepe University Faculty of Medicine, Department of Pediatric Nephrology.

The initial and follow-up clinical and laboratory information was recorded on a standardized form and entered into an on-site computerized database by centers. Data on each patient were obtained for: gender, age, duration of disease, blood pressure, clinical and laboratory characteristics at presentation, treatment, response to therapy, and outcome of renal function.

Definitions

The diagnosis of the nephrotic syndrome was defined according to the International Study for

Kidney Disease in Children (ISKDC)⁷. Steroid resistance was defined as failure to respond to treatment with oral prednisone at a dose of 60 mg/m² daily given for 4–6 weeks, followed by 60 mg/m² alternate day for 4 weeks. Treatment response was classified as: complete remission [reduction of proteinuria to 4 mg/m²/h or urine protein(mg)/creatinine(mg) ratio <0.5 with normal serum albumin]; partial remission [normal serum albumin (>3 g/dl) with persistent proteinuria (proteinuria 4-40 mg/m²/h or urine protein (mg)/creatinine (mg) ratio between 0.5 and 2)]; or no response [persistent proteinuria (proteinuria >40 mg/m²/h or urine protein/creatinine ratio >2)]. Recurrence of nephrotic range proteinuria in patients with complete or partial remission was defined as relapse. Hypertension was defined as a systolic and diastolic blood pressure above the 95th percentile on three consecutive measurements for age, gender, and height as published by the Second Task Force for Pediatric Hypertension⁸.

Renal insufficiency was defined as persistent rise in plasma creatinine (Pcr >1.5 mg/dl), and ESRD was defined as serum creatinine >5 times the normal upper limits or by the need for dialysis therapy.

Treatment Protocol

The standard regimen consisted of daily prednisone 2 mg/kg/d (maximum 60 mg/day), divided into two or three doses, for four weeks, followed by alternate-day prednisone for four additional weeks, and then tapered over a period of 2-3 months. Patient with partial or no response to prednisone were given oral cyclophosphamide (2 mg/kg/d for 8-12 weeks) or cyclosporin A (CsA) (3 mg/kg/d, for 4-6 months) in combination with low-dose oral prednisone (regime 1). Seventy-three patients received this regime. Thirty-three patients who did not respond to the initial regime were treated for up to 20 months using both pulse methylprednisolone (IVMP) and oral prednisone combined with cyclophosphamide, as proposed by Mendoza et al.⁹ (regime 2)

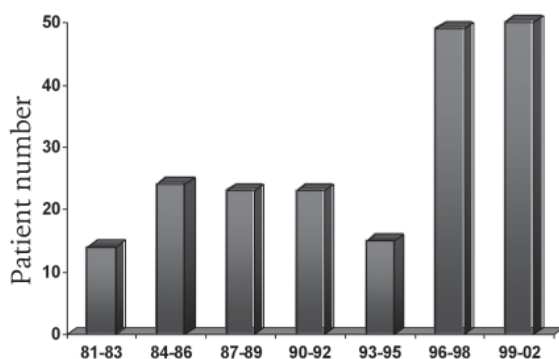


Fig. 1. Distribution of focal segmental glomerulosclerosis occurrence according to years.

Statistical Analysis

Statistics were reported as mean \pm SD for continuous variables and number (%) for categorical variables. Categorical variables were compared using the χ^2 test (or Fisher's exact test if expected count <5). Potential predictors or risk factors were included in the multivariate logistic regression model. Backward selection method was used to evaluate for potential predictors. All analyses were carried out using the computer package SPSS for Windows version 11. A value of $p < 0.05$ was considered significant.

Results

Clinical Characteristics

Data of 222 patients (92 boys; 130 girls) with FSGS were collected from 14 centers between 1981 and 2002. It seems that the number of patients with FSGS doubled between 1996 and 2002 when compared to the period between 1981 and 1995 (Fig. 1). The mean age at onset of patients was 8 years. The clinical and laboratory characteristics of children at

presentation are shown in Table I. Nephrotic syndrome was the presenting symptom in 89% of the patients. Edema was the most common feature. Hypertension was recorded in 37 patients (16%), and microscopic hematuria in 80 (36%). The mean Pcr and albumin levels were 0.82 ± 1.37 mg/dl and 2.38 ± 0.99 g/dl, respectively. Twenty-four patients (28%) had a Pcr >1.5 mg/dl.

Clinical Course

One hundred six patients were able to be assessed in terms of therapy. The median follow-up time of this group was 47.9 months (range: 0.26-270.5 months). Of them, 73 patients were treated with regime 1 and complete remission was recorded in 37% of the patients. In this cohort, 10% showed frequent relapses while 18% were steroid-dependent, and partial remission was noted in 35%. Progression to renal failure was observed in 28% of this patient group. In patients treated with regime 2 ($n=33$), complete remission, partial remission, no response and progress to renal failure were recorded in 51.5%, 27.3%, 12.1% and 9.1% of the patients, respectively. Renal survival was significantly worse in patients who received regime 1 when compared to those who received regime 2 (28% vs 9.1%, $p=0.02$).

The multivariate analysis demonstrated that only Pcr levels at presentation had an independent prognostic value for progressing to ESRD. Pcr >1.5 mg/dl was associated with a significantly poorer renal outcome than Pcr <1.5 mg/dl, regardless of the level of proteinuria (71.4% vs 27.6%, $p=0.027$). Patients with serum creatinine >1.5 mg/dl at presentation had 6.6 times (95% confidence interval [CI]: 5.4-7.8, $p < 0.001$) increased rate of progression to renal failure. The severity of proteinuria had

Table I. Patient Characteristics at Presentation

Clinical	Laboratory	
	N (%)	Mean \pm SD
Male/female	92/130	Serum creatinine (mg/dl) 0.82 ± 1.37
Edema	134 (81.7)	Serum albumin (g/dl) 2.38 ± 0.99
Hypertension	37 (16.7)	Urinary protein/creatinine (mg/mg) 12.9 ± 10.9
Hematuria	80 (49.1)	Triglyceride (mg/dl) 454.1 ± 415.1
Nephrotic syndrome	196 (89.4)	Cholesterol (mg/dl) 364.8 ± 162.6

no significant effect on progression to ESRD. No other clinical parameters studied, including age, gender and hypertension, were significant risk factors for prognosis.

Follow-up

One hundred forty-eight of 222 patients were followed-up for a median of 51 months (range 0.26-270 months) regardless of therapy given. At the end of follow-up period, the clinical course was characterized by sustained remission in 50 patients (33.8%) and persistent proteinuria in 50 (33.8%). Progression to renal failure was observed in a total of 48 patients (32.4%). Of them, 33 progressed to ESRD (17 under dialysis, 7 transplanted, 9 exitus) (Fig. 2). Overall progression to ESRD was significantly higher in patients who did not attain remission compared with those who attained remission (30.8% vs 5.6%, $p=0.008$).

Discussion

We have reported herein the largest retrospective nationwide cohort study of children with primary FSGS. Over the last 20 years, the incidence of FSGS in all age groups appears to be increasing, particularly in certain racial groups and ethnic populations. The reasons for this increase remain unknown. However, new etiological factors, possibly environmental, are thought to be involved¹⁰. In addition to these factors, this figure could also be related to the increasing number of pediatric nephrology centers and increasing number of biopsy procedures in Turkey. In one study, the diagnosis of FSGS in all pediatric kidney biopsies was 23% before 1990 and had increased to 47% thereafter. This increase was observed in all ethnic groups¹¹. Consistent with this observation, we also demonstrated a two-fold increase in the number of children with FSGS in recent years. We did not attempt to categorize our patients based on their socioeconomic status nor could we find an explanation for the observed high figure. Since there have been no changes in the genetic make-up of our pediatric population, we suggest that these changes in FSGS incidence might be related with environmental factors.

Most studies reported a mean age of 5-7 years at presentation^{12,13}. In the ISKDC study,

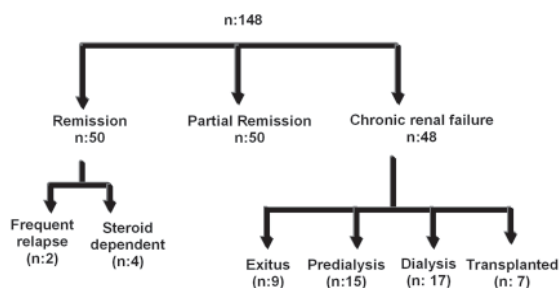


Fig. 2. Long-term outcomes of the patients.

the reported median age was 6 years for children with FSGS¹⁴. In our study, mean age at presentation was 8 years, and we could not demonstrate a predictor value of age at onset for chronic kidney disease, in contrast to a report by Abrantes et al.¹², who reported that age at onset >6.5 years for nephrotic syndrome was a strong predictor of chronic kidney disease.

The clinical features at presentation of our patients were not different from those of other series. Korbet et al.¹⁵ compiled data for 459 children with FSGS and reported the presence of nephrotic syndrome in 88%, hematuria in 54% and hypertension in 28% of patients. In the present study, 89% of the patients presented with nephrotic syndrome. Hypertension was recorded in 37 (16%) and microscopic hematuria in 80 (36%) patients.

A number of cohort studies of FSGS in children have been reported. Data from these series have shown that outcome is variable and that the progression to renal insufficiency occurs in 25% to 62% of patients^{4,16}. Persistent nephrotic range proteinuria, high serum creatinine at presentation, and steroid resistance are considered risk factors for progression to FSGS and chronic renal failure^{3,4}. Although the presence of nephrotic range proteinuria has consistently been associated with a poor prognosis in primary FSGS^{1,2}, several authors were unable to demonstrate that proteinuria at presentation was an independent predictor of ESRD^{5,12,17}. However, it is widely accepted that the prognosis in nephrotic patients with primary FSGS is significantly improved when remission of proteinuria is achieved^{3,5}. It has been reported that the prognosis for nephrotic FSGS patients who enter remission is excellent regardless of the histologic lesion⁶. In a series

of adult patients, Chun et al.⁶ showed an overall renal survival rate of 92% and 33% at 10 years for those patients who attained or did not attain remission, respectively. We observed that 30.8% of patients who did not achieve remission progressed to renal failure, in contrast with 5.6% of the patients who did achieve remission. Thus, achieving a remission significantly altered the course of our patients with FSGS. Our finding suggested that failure to achieve remission, not the severity of proteinuria at presentation, was a predictor of renal failure in children with primary FSGS.

Increased serum creatinine at presentation has been reported to indicate a poor prognosis in patients with FSGS^{12,17}. We also demonstrated that Pcr levels at presentation had an independent prognostic value for progression to ESRD. Moreover, patients with serum creatinine >1.5 mg/dl at presentation had 6.6 times increased rate of progression to renal failure.

Although corticosteroids are considered an accepted first-line therapeutic agent for children with FSGS, at best, 30% of the children with primary FSGS will achieve a complete remission with corticosteroids alone. In our series, a total of 73 patients received regime 1, and the rates of complete remission and partial response after the initial course of prednisone were 37% and 31.5%, respectively. This finding was similar to previous reports. In a study on a series of children and adolescents with FSGS, complete and partial remission were attained in 38.8% and 31.4%, respectively; however, only 14.5% patients received prednisone as a monotherapy during follow-up¹². Several therapeutic strategies have been applied in patients with steroid-resistant FSGS. These included alkylating agents and high-dose intravenous methylprednisolone in combination with either cyclophosphamide or chlorambucil and CsA in various dosages with or without prednisone^{18,19}. Alkylating agents have been used for treatment of steroid-resistant FSGS patients; however, their efficacy in inducing remission is not satisfactory. Reviews have documented that cyclophosphamide and similar agents may induce remission in only an extra 10% of those who do not respond to prednisone and are, therefore, of limited value^{15,20}. Tarshish et al.²¹ prospectively studied

patients with steroid-resistant FSGS randomly treated with prednisone or prednisone plus cyclophosphamide. The authors did not find any significant differences between the two groups regarding treatment failure and remission of proteinuria, and they concluded that cyclophosphamide therapy was not recommended for steroid-resistant FSGS.

Findings from the previous studies suggest that prolonged treatment with intravenous corticosteroids and oral cyclophosphamide is beneficial in patients with steroid-resistant FSGS^{9,22-24}. In the present study, 33 patients who did not respond to initial oral steroid therapy were treated for up to 20 months using both IVMP and oral prednisone combined with cyclophosphamide, as proposed by Mendoza et al.⁹ Long-term outcome in these patients was similar to that reported previously²⁴. Only 9% of patients who received Mendoza protocol reached end-stage renal failure. Findings from the present and previous studies suggest that prolonged treatment with intravenous corticosteroid and oral cyclophosphamide is beneficial in patients with primary FSGS.

In this cohort, long-term follow-up was available for 148 patients for a mean duration of 50 months. Overall, 67% of patients achieved a partial or complete remission as a result of all prescribed therapies, and complete remission was found to a predictor of an improvement in renal outcome. Our observations were compatible with the experiences of Chun et al.⁶ In contrast, Detwiler et al.²⁵ and Valeri et al.²⁶ found remission rates of less than 20% and overall progression to ESRD in 50% of patients over 2-3 years. The reason for the poorer response rates in these studies might be due to differences in therapeutic approach.

It has been reported that the remission rate after treatment is similar among patients with histologic variants, and that response to therapy can not be predicted on the basis of histology⁶. Furthermore, in a study on prognostic significance of renal histology, the multivariate analysis demonstrated that none of the histological features was independently significant as a predictor of ESRD¹⁷. In the present study, since our primary aim was to look for the impact of clinical parameters at presentation and response to treatment on long-term renal survival, we did not perform