Clinical Course of Children and Adolescents with Primary Focal Segmental Glomerulosclerosis and the Predictors of Their Outcome

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ABSTRACT:

BACKGROUND:

The aim of this retrospective study is to report the clinical course of children and adolescents with primary focal segmental glomerulosclerosis (FSGS), and to study their outcome and to identify the predictors of progression to end stage renal disease (ESRD).

PATIENTS AND METHODS:

This is a retrospective study of 50 patients with biopsy-proven primary FSGS who were admitted from April 1995 - January 2007, during the study period from May 2005 - June 2007. Clinical, Laboratory and histopathological data were recorded. The median follow-up time of 4.5 year.

RESULTS:

The commonest age and sex group is male between 1 - 5 year. At presentation all patients had nephrotic-range proteinuria, hypertension was noted in 22 (44%) of patients, microscopic haematuria was detected in 20 (40%) of patients, five patients had evidence of abnormal renal function. The distribution of patients according to steroid responsiveness show that the steroid sensitive patients were 21 (42%), 8 (38.09%) of them were frequent relapsers and 11 (52.38%) of them were steroid dependant and 2 (9.52%) of them developed secondary steroid resistance. But those who had steroid resistance from the start of treatment were 29 (58%) patients. During follow-up 30 (62%) patients had complete remission, 15 patients (30%) developed chronic kidney disease (9 of them stage 5).

At the end of follow-up, 24 (80%) of 30 patients with normal renal function had short stature. The univariate analysis identified the presence of hypertension (P=0.0027), heamaturia (P=0.0107) and presence of abnormal renal function (P=0.0001) at presentation, also presence of initial steroid resistance (P=0.0383), resistance to cytotoxic therapy (P=0.0032), capsular adhesions in renal biopsy (P=0.0066), tubular atrophy (P=0.0027), interstitial fibrosis (P=0.0010), all expect to be significant predictors of progression to ESRD.

CONCLUSION:

Considering the clinical and histological characteristics of studied patients, apparently our results are comparable to other published series. The progression to chronic kidney disease (CKD) occurs in 30% of patients after 5 years follow-up, must of them with ESRD, this is relatively good out come compared to other studies.

***KEY WARDS*:** focal segmental glomerulosclerosis, chronic kidney disease, end stage renal disease.

INTRODUCTION:

Focal segmental glomerulosclerosis (FSGS) is a clinicopathologic entity defined by the presence of proteinuria, often in the nephrotic range, and by segmental glomerular scars involving some but not all glomeruli and has a high risk of progressive loss of renal function [1]. Glomerulosclerosis is a general term to describe scarring of the Kidney's tiny blood vessels, the glomeruli, the functional units in the kidney that filter urine from the blood [2]. FSGS may be associated with several diseases or syndromes. In its idiopathic form, FSGS accounts for 10% of all children presenting with nephrotic syndrome (NS) [3]. The histologic features of idiopathic forms of FSGS were first described by Theodor Fahr in 1925 [4]. The incidence of FSGS appears to be rising, overall it is the cause of renal failure in about 2.5% of patients on renal replacement therapy [5, 6]. Clinical surveys from North America and the United Kingdom have reported the incidence of NS is between 2-4 new cases per 100000 children per year, with biopsy-

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confirmed FSGS comprising 15-20% of the total [7]. So there is a shift toward an increasing prevalence of FSGS over the years in the children [8]. The primary pathophysiologic process in FSGS is an injury to podocytes, which lead to fusion of the podocyte foot process with proliferation of mesangial, endothelial, and epithelial cells in the early stages followed by shrinkage and/or collapse of glomerular capillaries and ultimately, sclerosis [9].

PATIENTS AND METHODS:

The data were collected retrospectively from the records of the pediatric nephrology units at AL-Kathemia Teaching Hospital, AL-Karama Teaching Hospital and the Central Child Teaching Hospital. The study included 50 patients (children and adolescents) admitted from April 1995 to January 2007 with biopsy-proven primary FSGS, nephrotic syndrome, and minimum follow-up of 6 months. Patients with systemic diseases, history of reflux and hepatitis B infection or any other cause that might produce secondary FSGS were excluded, only the patients having "pure" idiopathic FSGS were taken.

The data reviewed were obtained at admission, at time of biopsy and at the end of follow-up are: Age, gender, age at onset of NS symptoms, height, weight, blood pressure, and response to steroid therapy, laboratory data (urea, creatinine, proteinuria, and hematuria).

Blood pressure was measured and standardized for age and gender using Task Force tables and the 95th percentile was used as the cut-off point.

All patients were submitted to a renal biopsy at a median age of 5 years (range: 1-16 years). During follow-up nine out of 50 patients were submitted to two renal biopsies and previous histological findings were minimal change in 4 patients and mesangial proliferative change in 5 patients.

The following features were recorded for each biopsy**:** the proportion of globally sclerosed glomeruli, proportion of glomeruli with segmental sclerosis, presence of mesangial expansion, capsular adhesions, tubular atrophy, and interstitial fibrosis.

During follow-up, GFR for each patient were estimated by the method of Schwartz et al. [10]. And the stages of CRF are determined according to the recent national kidney foundation (NKF) report and kidney disease outcomes quality initiative (K/DOQI) guidelines classification. Also the anthropometric measurements which includes body weight (kg) and height (cm) for children was taken. And body mass index (BMI) was calculated [11]. The data are presented on standard charts.

Treatment protocol:

PDN was started at a dose of 2 mg/kg/day or 60 mg/m^2/day (maximum daily dose: 80 mg) administered orally in divided doses for 4 weeks, followed by 4 weeks of the same dose given in a single dose every other day. After week 8, PDN was progressively tapered off at a rate of 25% a week until complete discontinuation by week 18-20. In children who failed to enter remission following 4 weeks of PDN therapy prescribed at 2 mg/kg/day or 60 mg/m^2/day, daily PDN was continued for a further 2weeks. And if also failed to enter remission, the term steroid resistant patients was given to them and renal biopsy was performed. Patients classified as steroid-dependent were given a low dose of PDN on alternate days on a long-term basis. Also those who had frequent relapses or steroid dependency and toxicity were received steroid sparing drugs like levamisole (2.5 mg/kg every other day), alkylating agents (cyclophosphamide and chlorambucil) and cyclosporine A. After performing the renal biopsy, steroid-resistant or steroid dependent patients received cyclophosphamide at the dose of 2 mg/kg for 12 weeks or 3 mg/kg for 8 weeks concurrently with low-dose PDN.

Since this is a retrospective study there was inevitable heterogeneity in the management of steroid resistant and cyclophosphamide non responder patients. Patients who did not respond to this initial regime were given chlorambucil or tacrolimus or MMF or methyl prednisolone i.v. plus oral administration of an alkylating agent, as proposed by Mendoza et al [12]. CsA was prescribed as the first immunosuppressive agent especially for children around puberty at an initial dose of 3-6 mg/kg/day in two divided doses for three months and then tapering continued for more than one year.

Definitions:

The definition of chronic kidney disease (CKD) is: an estimated glomerular filtration rate (GFR)<60 ml / min in two consecutive tests. GFR was estimated by the method of Schwartz et al. . GFR stage 5 was defined as a GFR <15 ml / min or the need for renal replacement therapy.

Schwartz et al. formula for calculation of GFR:

$GFR = K \times Height / P_{creat.}$ Values of K are different in various age groups**.**

Statistical analysis:

All data were coded and entered to the computer. Data arranged and tabulated by using statistical package for social science (SPSS).

Univariate analysis to detect the relationship between each clinical, histological parameters and

response to therapy and progression to ESRD was performed by using Chi-square test as the standard statistical test. p. value < 0.05 considered to be significant.

RESULT:

A total of 50 patients were included in the study. Thirty four were males (68%) and 16 (32%) were females.

The median age at presentation for patients was 5 years (range: 1 - 15 years),

The Distribution of patients with FSGS according to age at presentation is shown in table (1).

The commonest age group is male between 1 - 5 year.

At presentation all patients had nephrotic-range proteinuria, hypertension was noted in 22 (44%) of patients while microscopic haematuria was detected in 20 (40%) of patients and none of these patients had macroscopic haematuria at presentation, five patients had evidence of abnormal renal function at diagnosis.

The distribution of patients with FSGS according to steroid responsiveness is shown in table (2).

All were submitted to a renal biopsy at a median age of 5 years (range: 1 - 16 years). The number of glomeruli per biopsy ranged from (7 - 40).

Histological data at the time of biopsy were recorded for all patients show that 24 patients (48%) had segmentally sclerosed glomeruli > 20% of total glomeruli ranging from (16-22%), 10 patients (20%) had globally sclerosed glomeruli >10% of total glomeruli ranging from (8-14%), 15 patients (30%) had mesangial expansion, 19 patients (38%) had capsular adhesions, 22 patients (44%) had tubular atrophy and 20 patients (40%) had interstitial fibrosis.

The Median follow-up time was 4.5 years (range: 6 months-10 years).

The initial responses to individual immunosuppressive therapies are shown in table (3).

The distribution of patients according to the outcome is shown in diagram (1).

Growth parameters:

Height was obtained in 30 patients with normal renal function at the end of follow-up. At admission 3 patients only below the 5th centile, and at end of follow-up only 6 patients ≥ 5th centile. So 24 (80%) patients had short stature, 15 patients of them had history of steroid responsiveness and 9 patients had history of steroid resistance.

BMI for age calculated at end of follow-up also in 30 patients with normal renal function. 23 (76.6%) patients had a normal BMI for age (above the 5th centile and below the 85th centile), 4 (13.3%) patients had risk for overweight (BMI for age between 85th centile and 95th centile), and 3 (10%) patients had overweight (BMI > 95th centile).

Predictors of outcome of children with FSGS:

The correlation between clinical and histological features and ESRD is shown in table (4).

The univariate analysis identified the correlation between clinical and histological features and progression to ESRD, presence of hypertension and haematuria at presentation were significant predictors of progression to ESRD (P= 0.0027 and 0.0107 respectively), also presence of abnormal renal function at presentation (P= 0.0001), initial steroid resistance (P= 0.0383), resistance to cytotoxic therapy (P= 0.0032), presence of Capsular adhesions in the renal biopsy (P= 0.0066), tubular atrophy (P= 0.0027), interstitial fibrosis (P= 0.0010). All expect to be significant predictors of progression to ESRD.

But initial steroid responsivness (P=0.5657), response to cytotoxic therapy (No correlation), presence of mesangial expansion in renal biopsy (P= 0.2965), presence of segmentally sclerosed glomeruli > 20% (p=0.5598), globally sclerosed glomeruli > 10% (P=0.2696). None of them expect to be as predictors of progression to ESRD.

DISCUSSION:

A retrospective study of children and adolescents with primary FSGS followed for a median time of 4.5 years (range: 6 months-10 years). There is a limitation associated with the retrospective design of the study. Nevertheless, the present study involves adequate number of children and adolescent with FSGS and about half of the cohort was followed for more than 5 years.

A number of cohort studies of FSGS in children have been reported [13-16]. Data from these series have shown that outcome is variable and progression to renal insufficiency occurs in 25% [14] to 62% [16]. In this study the findings suggest that 15 patients (30%) presented with deterioration of renal function after 5 years follow-up most of them (9 patients) had stage 5 CKD, nearly what shown by Martinelli et al. [14], they pointed out that the reasons for the relatively good survival rate in their study were not clear. They suggested that in most reports the mean observation time has been relatively short and the number of patients were few similar to our study.

The clinical features at presentation of the sample are not very different from those of other series. Marcelo et al. [15] compiled data for 110 children and adolescent with FSGS and showed that there was a predominance of males (64.5%), nephrotic syndrome (88%), haematuria in (38.2%) and (50%)

with blood pressure levels above the 95th percentile for age and gender. In this cohort, there was also a preponderance of males (68%), nephrotic syndrome in (100%), haematuria in (40%) and hypertension in (44%).

Data from previous studies have shown that the median age at presentation ranges from 5 years [17] to 12 years [13], in this study the median age at presentation was 5 years, so it is younger age as in the study with more favorable outcome, the median age at presentation was also younger [17].

The initial response to conventional doses of corticosteroid therapy for idiopathic FSGS is poor in contrast to that of minimal change disease (MCD) [18]. In the majority of studies published, the response rate has been less than 30% [19]. The result of this study demonstrate that 21 (42%) patients were steroid sensitive initially and this is a good percentage.

This data shows that the stature of patients who continued to have normal renal function was affected, possibly due to the growth-inhibitory effects of prolonged courses of steroid therapy [20]. At the end of follow-up about one half of this cohort presented with stature below the 5th centile-while in previous study of Marcelo et al. [15] from 110 patients of FSGS, twenty three patients (27.7%) presented with short stature. This finding calls attention to the necessity to improve treatment regimen for children and adolescents with FSGS.

Previous studies addressing the efficacy of cyclophosphamide in inducing remission showed conflicting results [19]. A controlled trial looking at the efficacy of oral cyclophosphamide therapy in inducing remission in FSGS failed to demonstrate a benefit over the placebo therapy [21]. However, many case cohorts studied have reported variable beneficial effects [14, 19]. The results of this study demonstrate that a single course of oral cyclosphosphamide induced remission in 68.75% of patients with FSGS when used as the first cytotoxic agent and thus supports the use of cyclophosphamide in FSGS. This result is nearly what demonstrated by Asiris. Et al. [22] that a single course of oral cyclophosphamide induced remission in 43.1% of patients with FSGS when used as the first cytotoxic agent. However, there is currently an options regarding the optimal therapy for patients with steroid-resistant NS and the best available evidence supports the use of cyclosporine A [19, 23].

In this study, 16 patients who received cyclosporine A as the first immunosuppressive therapy, remission was induced in 50% of patients. This result is nearly what demonstrated by Asiris. et al. [22] that used cyclosporine A as the first immunosuppressive therapy in 15 patients and induced remission in 40% of them. However, long-term cyclosporine A therapy is associated with potential nephrotoxicity, while the histological changes are indistinguishable from the progression to FSGS and therapy makes it difficult to quantity the risk of nephrotoxicity [23].

Regarding the predictors of progression to ESRD, previous studies suggested that the initial response to corticosteroids has been regarded as a powerful predictor of renal survival; resistance to corticosteroids has been shown to be an important predictor of progression to ESRD [19].

A correlation between poor outcome and mesangial expansion has been described [24]. Moreover, another study group recently described glomerular tip lesions an independent predictor of good renal outcome [25]. Also Asiris et al. [22] described renal impairment at presentation as predictor of poor outcome. Tejani et al. [16] reported that the patient's response to immunosuppressants affected prognosis. If no remission was achieved with both cyclophosphamide and CsA, the patients would experience a lack of edema control and a poor renal prognosis [16].

In primary idiopathic FSGS with nephrotic range proteinuria patients who achieve a remission have a significantly improved clinical course, in that, the progression to ESRD is less than 15% [3]. In contrast, over 60% of those fail to achieve remission progress to ESRD [3].

In this study the presence of hypertension, haematuria and abnormal renal function at presentation; initial steroid resistance and resistance to cytotoxic therapy; presence of capsular adhesions, tubular atrophy and interstitial fibrosis in the renal biopsy were considered to be an important predictors of progression to ESRD.

CONCLUSION:

Considering the clinical and histological characteristics of the present patients, apparently the cohort of idiopathic FSGS is comparable to other published series. The progression to CKD occurs in (30%) of patients after 5 years follow-up most of them with ESRD, this is relatively good outcome compared to other studies. Possibly, discrepancies in the size of the cohort, time of follow-up. May explain this difference in the rate of outcome.

As half of the patients developed short stature, this finding calls attention to the necessity to improve treatment regimes for children and adolescents with FSGS also to look for other causes of short stature and the need for growth hormone therapy

prior to transplantation.

More intensive immunosuppressive regimens must emerge on the basis that the non-responding patient would finally have to undergo a renal transplantation resulting in life-long immunosuppressive therapy in addition repeated courses of cytotoxic therapy would increases the risk of future malignancies and gonadal toxicity and possibly increase the risk of post-transplant lymphoproliferative disease.

We must encourage the histopathologist to focus on histological variant (tip lesion, collapsing, cellular) during examination. Also immunoflurescence and electron microscope examination of the specimen must encourage.

Table (1): Distribution of patients with FSGS according to age at presentation

Age (year)	male	female	total	%
1-5	22	10	32	64
6-10	8	5	13	26
11-15	4	1	5	10
total	34	16	50	100

Table (2): Distribution of patients with FSGS according to steroid responsiveness

Patients	No.	%
Steroid sensitive nephrotic syndrome	21	42
a- Frequent relapsers	8 (38.09%)	
b- Steroid dependent nephrotic syndrome	11 (52.38%)	
c- Secondary resistance	2 (9.52%)	
Steroid resistant nephrotic syndrome	29	58
total	50	100

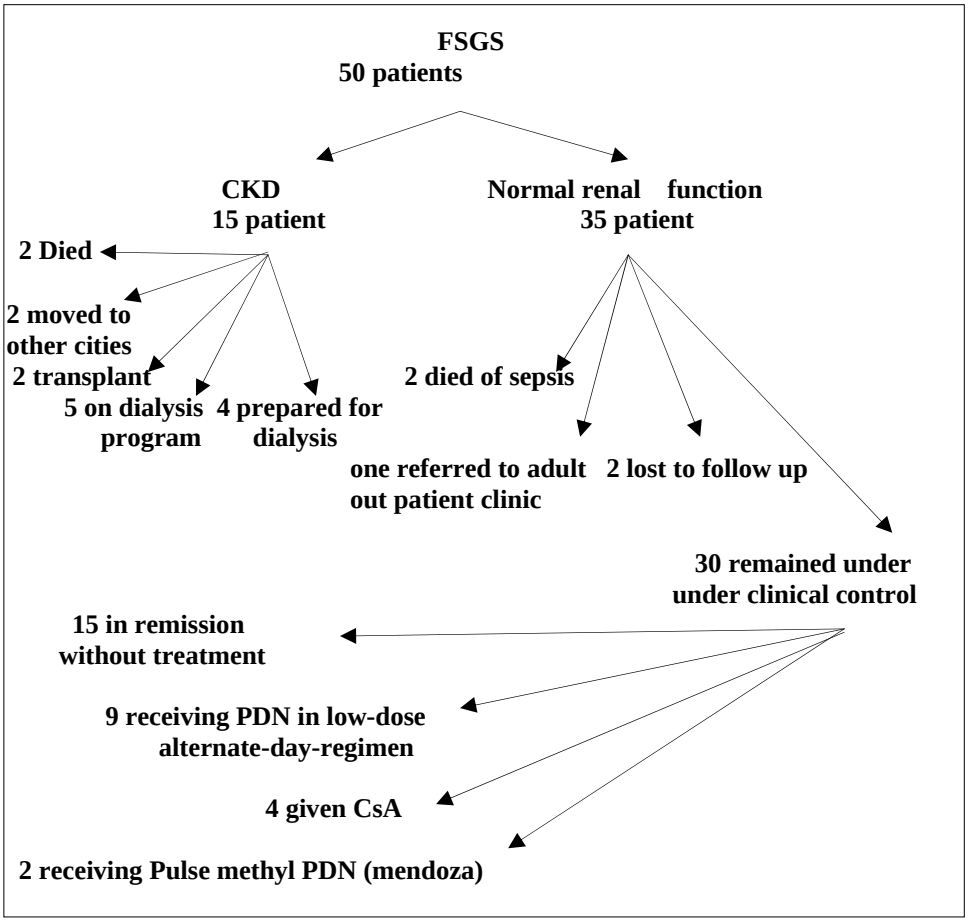
Table (3): Response to immunosuppressive therapy

	Total (n=50)	ESRD at 5 years (n=9)	x^2	P value
Hypertension at presentation	22	8	8.97	0.0027
Haematuria at presentation	20	7	6.52	0.0107
Abnormal renal function at presentation	5	5	25.30	0.0001
Initial steroid responsivness	21	3	o.33	0.5657
Initial steroid resistance	29	8	4.29	0.0383
Response to cytotoxic therapy	30	0	No correlation	
Resistance to cytotoxic therapy	18	9	19.5	0.0032
Segmental sclerosis >20%	24	5	0.34	0.5598
Globally sclerosed glomeruli >10%	10	3	1.219	0.2696
Mesangial expansion	15	4	1.09	0.2965
Capsular adhesions	19	7	7.37	0.0066
Tubular atrophy	22	8	8.97	0.0027
Interstitial fibrosis	20	8	10.9	0.0010

Table (4): Correlation between clinical and histological features and ESRD

Drug	cyclophosphamide	cyclosporine A	Pulse methyl prednisolone
Number of patients	32	14	2
Complete remission	22 (68.75%)	7 (50%)	1 (50%)

Diagram (1): Distribution of patients according to the outcome.



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