SHORT COMMUNICATION

Idiopathic Focal Segmental Glomerulosclerosis

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This study was conducted to determine the prognostic value of some clinical, laboratory, histopathologic and therapeutic factors in 62 children with focal segmental glomerulosclerosis. There were no significant differences between the factors studied, except for severe interstitial fibrosis, which was more frequent in patients with chronic kidney disease (P=0.03). The prevalence of chronic kidney disease in non-responder groups was significantly higher (P<0.05). We found therapy with cyclophosphamide to be promising in patients with focal segmental glomerulosclerosis.

Key words: *Focal segmental glomerculosclerosis, Iran, Nephrotic syndrome, Prognosis.*

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The diagnosis of focal segmental glomerculosclerosis (FSGS) is based on findings on light microscopy examination, including sclerosis of glomeruli and involvement of only a portion of the capillary tuft. On immunofluorescence examination, the segmental lesions may show strong staining for IgM and C3(1, 2). Occasional cases of familial FSGS have been reported(3). Patients with steroid resistant nephrotic syndrome (SRNS) are at risk for developing end stage renal disease(2). We conducted this study to determine the prognostic value of clinical, laboratory, histopathologic and therapeutic factors in children with FSGS.

METHODS

Of 99 patients with idiopathic FSGS seen at this center during 1986 to 2002, 62 were included. All patients had features of nephrotic syndrome, only patients with a minimum follow up of 5 yr or estimated glomercular filtration rate (GRF) ≥75 mL/min/1.73 m^2 were included(4). Thirty seven patients who did not return for follow up visits were excluded. Secondary FSGS was excluded based on history, clinical, serologic and immunofluorescence examination findings and imaging studies. Hematuria was defined by presence of ≥5 red cells/HPF and hypertension as systolic or diastolic blood pressure more than 95th percentile for age and gender(5).

Steroid responder was defined as: (*i*) patients in remission following treatment with prednisone or prednisolone at a dose of 2 mg/kg daily for 4 weeks, (*ii*) remission following therapy with cyclophosphamide (2 mg/kg for 12 weeks or 3 mg/kg for 8 weeks); or (*iii*) remission after therapy with cyclosporine (5 mg/kg daily for 12 months). Remission was defined as no proteinuria for 3 consecutive days or 24-hour urine protein excretion <4 mg/m^2/h. Chronic kidney disease was defined as an abnormality of kidney function which has been present for 3 or more months(6). Comparison between patients who were non-responder and responder was done using chi-square test, Fisher's exact or Mann-Whitney tests; P<0.05 was considered significant.

All patients received prednisolone or prednisone

at a dose of 2 mg/kg daily for 4 weeks, then 2 mg/kg every other day 4 weeks which was tapered slowly in 3-6 months. Twelve patients underwent kidney biopsy before starting treatment due to gross hematuria, sustained hypertension, evidence of azotemia or age ≤1 yr and others after treatment with steroid due to steroid unresponsiveness or if they were considered for treatment with cyclophosphamide or cyclosporine. In patients with steroids resistance, cyclophosphamide was used. Patients whose parents did not consent for treatment with cyclophosphamide received cyclosporine with prednisolone (0.1-0.5 mg/kg on alternate days). We used cyclosporine in patients with cyclophosphamide resistance or relapse of disease after cyclophosphamide withdrawal.

RESULTS

Thirty six patients (58%) were ≤6 year old and 24 (38.7%) were >6 year; 41 (66.1%) were boys. The mean (range) of follow-up was 7.2 (0.25-16.3) year. Twenty five patients (40.3%) were steroid sensitive and rest were steroid resistant. ***Table* I** shows variables in steroid resistant and steroid sensitive patients. Twelve of 35 patients (34.3%) responded to cyclophosphamide and 2 of 16 (12.5%) responded to cyclosporine. There was no correlation between age at onset, gender, presence of hematuria or hypertension at presentation and histopathologic findings with outcome.

Histologic specimens were reviewed for proportion of glomeruli showing segmental

TABLE I CORRELATION BETWEEN CLINICAL FEATURES AND OUTCOME IN IDIOPATHIC FSGS

Variable	Steroid Sensitive Group 1	Steroid Resistant Group 2	Renal function on last follow-up			
			Normal renal function		Chronic kidney disease	
	(*n*=25)	(*n*=37)	Group 1 (*n*=22)	Group 2 (*n*=15)	Group1 (*n*=3)	Group 2 (*n*=22)
Age ≤ 6 yr	20	17	17	6	3	11
Age > 6 yr	5	18	5	9	0	9
Males	18	23	15	11	3	12
Hypertensive	4	8	3	2	1	6
Hematuria	7	20	7	6	0	14
Renal histology=						
Hilar FSGS	9	6	8	3	1	3
Tip FSGS	5	12	4	5	1	7
Non-specified FSGS	4	7	4	3	0	4
Collapsing FSGS	2	10	1	3	1	7
Mild to moderate glomerulosclerosis	19	29	16	13	3	16
Severe glomerulosclerosis	1	6	1	1	0	5
No tubular atrophy	2	4	2	2	0	2
Mild to moderate tubular atrophy	16	24	13	10	3	14
Severe tubular atrophy	2	7	2	2	0	5
No interstitial fibrosis	1	4	1	2	0	2
Mid to moderate interstitial fibrosis	17	21	14	10	3	11
Severe interstitial fibrosis	2	10	2	2	0	8

** The age at onset of two patients was unknown. † Immunofluorescence microscopy examination was done in 34 patients and detailed review of renal histopathology in 55.*

WHAT THIS STUDY ADDS?

- Therapy with cyclophosphamide is promising in patients with steroid resistant focal segmental glomerulosclosis.

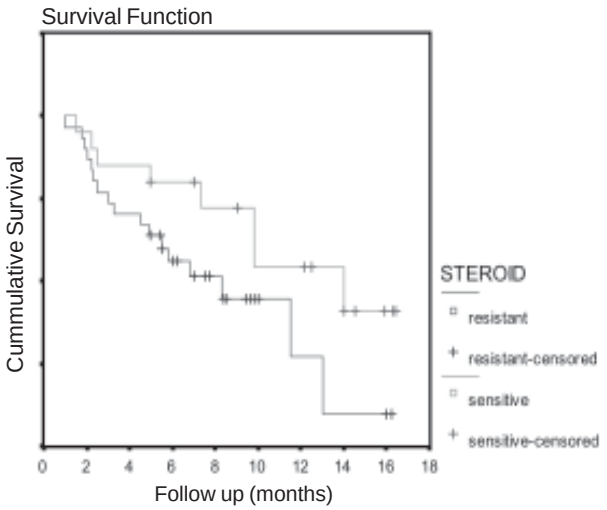
glomerulosclerosis, interstitial fibrosis, tubular atrophy and types of FSGS (tip, hilar, collapsing and non-specified types). Severe interstitial fibrosis was found (*P*=0.03) in patients whose diseases progressed to chronic kidney disease. Patients showing steroid resistance or non-response to cyclophosphamide were significantly more likely to show deranged renal functions (*P*=0.0002 and *P*=0.003, respectively). ***Fig.* 1** shows renal survival in steroid sensitive *versus* steroid resistant FSGS**.** Relative risks for renal dysfunction in steroid, cyclophosphamide and cyclosporine non-responders were 2.17 (95% confidence interval (CI) 1.43-3.29), 3.13 (95% CI 1.49-6.59) and 2.33 (95% CI 1.27-4.27), respectively.

DISCUSSION

Ostalska, *et al*.(7) reported a less favorable clinical course in children <1 year of age. The clinical course has been suggested to be satisfactory if sclerotic lesions are peripheral, although these findings have not been confirmed by others(8). Renal survival has been directly associated with degree of proteinuria(9). Cyclophosphamide may have some survival benefits in those with at least a partial response measured by impact on proteinuria and progression to ESRD(10), but a randomized trial showed that there was no difference in renal survival after cyclophosphamide treatment(11).

It is suggested that therapy with alkylating agents might not be useful for treatment of primary FSGS. Patients in this study showed a relatively better response to cyclophosphamide and 34.3% reached complete remission. Two out of 12 (16.2%) patients who were cyclophosphamide responsive and 17 out of 23 (73.9%) non responders showed progression of renal dysfunction.

Paik, *et al*.(12) showed that asymptomatic proteinuria at presentation, initial renal insufficiency; higher segmental sclerosis, severe tubulointerstitial changes, initial non-responder and absence of remission are poor prognostic factors. Another study reported a renal survival rate of 90% in responders while in non-responders it was 48%(13). In our study, renal survival rates for steroid, cyclophosphamide and cyclosporine responders were 88%, 83.8% and 100%, respectively. Findings from this study suggest that satisfactory responses to therapy with steroids and cyclophosphamide results in improved long term outcome.



	Total	number events	number censored	percent censored
Steroid sensitive	25	8	17	68
Steroid sensitive	37	17	20	54

FIG. 1 *Kaplan Meir graph showing renal survival outcome in steroid sensitive versus steroid resistant FSGS.*

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