Correlation between Prognosis and Response to Treatment in Children with Focal Segmental Glumerulosclerosis

Mitra Naseri[1*], Abbas Madani[2], and Neamatollah Ataei[2]

[1] *Department of Nephrology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2] *Department of Pediatric Nephrology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

Received: 8 Oct. 2007; Received in revised form: 5 Nov. 2007; Accepted: 19 Jan. 2008

Abstract- To determine the prognostic value of response to treatment in patients with focal segmental glomerulo-sclerosis. FSGS includes 10-15% of idiopathic Nephrotic syndrome in children. Bulk of evidence supports disease relationship with immune system. Unfortunately, responses to immunosuppressive drugs are not desirable and progression to end-stage renal disease is common. We analyzed 62 out of 99 cases of biopsy proven idiopathic FSGS who were followed for at least 5-years or until renal failure occurred during study. Study design was historical cohort and patients were divided into two groups: exposed (resistant to treatment) and non-exposed (responsive to treatment). Correlation between prognosis and response to treatment was statistically evaluated. P-value (0.05 and relative risk (1 was considered significant. In 3 out of 25 steroid responsive patients (12%) and 22 out of 37 steroid resistant patients (59.5%), disease progressed to renal failure. Disease progressed to renal failure in 2 out of 11 cyclophosphamide responsive patients (18.1%), 17 out of 23 cyclophosphamide resistant patients (74.3%), and 8 out of 14 cyclosporine resistant patients (57.1%). 2 patients who responded to cyclosporine had normal renal function at the time of the last follow up. We concluded that favorable response to steroid and cyclophosphamide treatment is a protective factor against disease progression to end stage renal disease and resistance to these drugs imply a poor prognosis. For making any definite conclusion concerning response to cyclosporine treatment and prognosis, similar studies with a larger sample are required.

Acta Medica Iranica 2009; 47(2): 93-96.

Key words: Children, nephrotic syndrome, glomerulosclerosis, focal segmental, drug resistant, prognosis, steroids.

Introduction

Focal Segmental Glomerulosclerosis (FSGS) includes 10-15% of idiopathic nephrotic syndromes in children. Although pathogenesis is unknown, new studies suggest the role of podocytes disturbances in pathogenesis of disease (1). Recent data demonstrate differences between the basic pathophysiology of FSGS and minimal change nephrotic syndrome (MCNC). FSGS appears to be a podocytes disease (2). Although several published papers show a relationship between disease and immune system, response to immunosuppressive drugs is variable. FSGS includes 3% of steroid sensitive and 47.5% of steroid resistant idiopathic nephrotic syndrome (3). Clinical symptoms in FSGS are nonspecific and include edema, hypertension and sometimes gross hematuria. Urine analysis shows proteinuria with or without hematuria. The glomerular lesions affect a variable proportion of glomeruli. Focal changes are limited to a part of glomerular tuft and segmental lesions affect a few capillary loops (3-6).

Tubular atrophy and interstitial fibrosis are often present (3,4,7). On immunofluorescence, the segmental lesions may show strong staining with anti-IgM and anti C3 anti-sera. Familial cases have been reported with autosomal dominant modes of inheritance (8-10). Different immunosuppressive drugs may be used for treatment including glucocorticoids, cyclophosphamide, cyclosporine, methyl prednisolone pulse, chlorambucil and recently FK506 (3,11-16). Patients with steroid resistant nephrotic syndrome (SRNS) are at risk for developing end-stage renal disease (ESRD).

ESRD developed in at least 50% of patients with SRNS.3 Progression to ESRD has been reported to be more rapid in patients of African or Hispanic descent when compared with whites (17).

Corresponding Author: Mitra Naseri
Department of Nephrology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 511 7269021-5, Fax: +98 511 7277470, E-mail: mtr_naseri2006@yahoo.com

Table 1. Response to steroid and prognosis

Response to treatment	Renal failure		Good renal function		Total	
	Number	Percent %	Number	Percent %	Number	Percent %
Steroid sensitive	3	12	22	88	25	100
Steroid resistant	22	59.5	15	40.5	37	100
Total	25	40.3	37	59.7	62	100

P-value = 0.00019

Patients and Methods

We prospectively studied 62 patients with biopsy proven idiopathic FSGS admitted to pediatric medical center of Tehran between 1986- 2002.

The patients(ages were between 3 months to 14 years (mean age 4 years and 8 months). 24 patients were female and 38 patients were male (M/F= 1.6/1)

All patients were followed for at least 5 years or until renal failure occurred during follow up. The patients were followed for a period between 3 months to 16 years and 4 months (mean 7 years and 2 months).

As the first line treatment, all patients received prednisolone 2 mg/kg daily for 4 weeks (before or after renal biopsy) and subsequently 2 mg/kg in alternate days which was tapered slowly in 3 to 6 months. In steroid resistant patients after obtaining informed consent from the parents, cyclophosphamide was administered at the dosage of 2 mg/kg for 12 weeks or 3 mg/kg for 8 weeks. We prescribed cyclosporine at the dosage of 5 mg/kg daily for 12 months in conjugation with low dose steroid to 3 groups of patients: those whose parents failed to accept cyclophosphamide (mainly because of gonadal toxicity), steroid dependent patients, steroid and cyclophosphamide resistant patients.

Patients were followed by nephrology clinic at first weekly, then every other week or monthly and every 1-3 months after remission.

In each visit, the patients were checked for edema, hypertension and infection and urine samples were analyzed for proteinuria by dipstick-test. If proteinuria was present, 24 hour urine proteins or protein-creatinine ratio in random urine samples were measured. Serum creatinine was checked every 3-6 months. In patients who received cyclosporine, serum creatinine level checked weekly in the first month, then every 2 weeks for 6 months and monthly afterward.

The study design was historical cohort and the patients were divided into two groups:

Exposed group (resistant to treatment) and non-exposed group (sensitive to treatment).

Correlation between variables (response to steroid, cyclophosphamide and cyclosporine) and prognosis was statistically analyzed. P-value (0.05 and relative risk (1 was considered significant.

We defined normal renal function at final follow- up as good prognosis and decreased renal function (permanent rising of serum creatinine level) as poor prognosis. The patients were considered cyclophosphamide or cyclosporine resistant if proteinuria continued after a full course of treatment.

Results

25 out of 62 patients (40.3%) were steroid sensitive and 37 out of 62 patients (59.7%) were steroid resistant. 35 out of 62 patients received cyclophosphamide of whom 12 (34.2%) and 23 (65.8%) were cyclophospohamide sensitive and cyclophospohamide resistant respectively. 16 out of 62 patients received cyclosporine of whom 2 (12.5%) responded to cyclosporine and 14 (87.5%) were cyclosporine resistant. Table 1-3 and figure 1 show the correlation between renal function and response to treatment. Comparison between drug responsive and drug resistant groups showed statistically significant difference (P-value for steroid, cyclophospohamide and cyclosporine were 0.00019, 0.00346 and 0.46 respectively). Relative risk of renal failure in steroid and cyclophospohamide resistant patients were greater than 1(RR>1). Table 4 shows patients at final follow-up

Table 2. Response to cyclophosphamide and prognosis

Response to treatment	Renal failure		Good renal function		Total	
	Number	Percent %	Number	Percent %	Number	Percent %
Cyclophosphamide sensitive	2	16.1	10	83.3	12	100
Cyclophosphamide resistant	17	73.9	6	26.1	23	100
Total	19	54.3	16	45.7	35	100

P-value = 0.00346

Table 3. Response to cyclosporine and prognosis

	Renal failure		Good renal function		Total	
Response to treatment	**Number**	**Percent %**	**Number**	**Percent %**	**Number**	**Percent %**
cyclosporine sensitive	0	0	2	100	2	100
cyclosporine resistant	8	57.1	6	42.9	14	100
Total	8	50	8	50	16	100

P-value = 0.466

Table 4. Clinical course of the disease in our patients

Clinical course	**Number**	**%**
Complete remission	23	37
Persistent NS + normal renal function	14	22.6
CRF (needed to symptomatic treatment)	2	3.2
ESRD	14	22.6
Kidney transplantation with good graft function	5	8.1
Death Due to complications of renal failure	4	6.5
Total	62	100

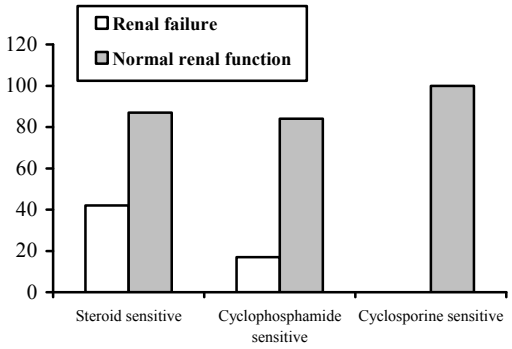

Figure 1. Response to treatment and prognosis

Discussion

In the early stage, FSGS and MCNS are indistinguishable (18) and a significant number of patients with FSGS respond favorably to glucocorticoid therapy (19).

Different studies have been conducted to clarify different therapeutic factors that affect outcome in patients with nephrotic syndrome.

It has been shown that response to steroid therapy carries a greater prognostic value than the histological features seen on the initial renal biopsy (20,21).

Hafeez et al reported a limited response to cyclosporine in patients with FSGS (22). On the contrary, other studies showed that a more prolonged use of corticosteroid and early introduction of cyclosporine A may improve the prognosis for primary FSGS and suggested cyclosporine A as a good therapeutic option for SRNS (21-23).

Lyengar reported higher risk of CRF in patients who didn't respond to cyclosporine A (24) and Geary reported less frequency of renal failure in patients who responded to cyclophospohamide (15) Other studies have reported resistance to steroid or cyclosporine as poor prognostic factors (19,20).

Our study showed that renal failure is significantly more frequent in steroid and cyclophospohamide resistant patients ($P<0.05$) and positive response to these drugs improved the prognosis dramatically. So we suggest steroid in all cases of FSGS and cyclophospohamide in steroid resistant cases as the second step of treatment despite its gonadal toxicity. About correlation between cyclosporine response and prognosis, Because of the small sample of patients who received cyclosporine, we cannot draw a clear conclusion considering the value of cyclosporine in FSGS patients. Further studies with a larger sample of patients are recommended.

Acknowledgments

Authors would like to thank Dr. Sadeghi for grammatical correction of paper.

References

1. Hara M, Yanagihara T, Kihara I. Urinary podocytes in primary focal segmental glomerulosclerosis. Nephron 2001; 89(3): 342-7.
2. Raats CJ, van den Born J, Berden JH. Glomerular heparin sulfate alterations: mechanisms and relevance for proteinuria. Kidney Int 2000, 57: 385-400.
3. Niaudet P. Steroid-resistant idiopathic nephrotic syndrome in children. In: Niaudet P, Avner ED, Harmon WE, editors. Pediatric Nephrology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 557-73.

4. Habib R. Editorial: Focal glomerular sclerosis. Kidney Int 1973; 4(6): 355-61.
5. Habib R, Kleinknecht C. The primary nephrotic syndrome of childhood. Classification and clinicopathologic study of 406 cases. Pathol Annu 1971; 6: 417-74.
6. Churg J, Habib R, White RH. Pathology of the nephrotic syndrome in children: a report for the International Study of Kidney Disease in Children. Lancet 1970; 760(1): 1299-302.
7. Jenis EH, Teichman S, Briggs WA, Sandler P, Hollerman CE, Calcagno PL, et al. Focal segmental glomerulosclerosis. Am J Med 1974; 57(5): 695-705.
8. Mathis BJ, Kim SH, Calabrese K, Haas M, Seidman JG, Seidman CE, et al. A locus for inherited focal segmental glomerulosclerosis maps to chromosome 19q13. Kidney Int 1998; 53(2): 282-6.
9. Kaplan JM, Kim SH, North KN, Rennke H, Correia LA, Tong HQ, et al. Mutations in ACTN4, encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis. Nat Genet 2000; 24(3): 251-6.
10. Winn MP, Conlon PJ, Lynn KL, Howell DN, Gross DA, Rogala AR, et al. Clinical and genetic heterogeneity in familial focal segmental glomerulosclerosis. International Collaborative Group for the Study of Familial Focal Segmental Glomerulosclerosis. Kidney Int 1999; 55(4): 1241-6.
11. Mendoza SA, Reznik VM, Griswold WR, Krensky AM, Yorgin PD, Tune BM. Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agents. Pediatr Nephrol 1990; 4(4): 303-7.
12. Tune BM, Kirpekar R, Sibley RK, Reznik VM, Griswold WR, Mendoza SA. et al. Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: a long-term follow-up. Clin Nephrol 1995; 43(2): 84-8.
13. Ingulli E, Singh A, Baqi N, Ahmad H, Moazami S, Tejani A. Aggressive, long-term cyclosporine therapy for steroid-resistant focal segmental glomerulosclerosis. J Am Soc Nephrol 1995; 5(10): 1820-5.
14. Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. J Am Soc Nephrol 1996; 7(1): 56-63.
15. Geary DF, Farine M, Thorner P, Baumal R. Response to cyclophosphamide in steroid-resistant focal segmental glomerulosclerosis: a reappraisal. Clin Nephrol 1984; 22(3): 109-13.
16. Safety and tolerability of cyclosporin A (Sandimmun) in idiopathic nephrotic syndrome. Collaborative Study Group of Sandimmun in Nephrotic Syndrome [editorial]. Clin Nephrol 1991; 35 Suppl 1: S48-60.
17. Ingulli E, Tejani A. Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. Pediatr Nephrol 1991; 5(4): 393-7.
18. Kashgarian M, Hayslett JP, Siegel NJ. Lipoid nephrosis and focal sclerosis distinct entities or spectrum of disease. Nephron 1974; 13(2): 105-8.
19. Habib R. Editorial: Focal glomerular sclerosis. Kidney Int 1973; 4(6): 355-61.
20. Niaudet P. Steroid-resistant idiopathic nephrotic syndrome in children. In: Niaudet P, Avner ED, Harmon WE, editors. Pediatric Nephrology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 543-56.
21. Paik KH, Lee BH, Cho HY, Kang HG, Ha IS, Cheong HI, et al. Primary focal segmental glomerular sclerosis in children: clinical course and prognosis. Pediatr Nephrol 2007; 22(3): 389-95.
22. Hafeez F, Ahmad TM, Anwar S. Efficacy of steroids, cyclosporin and cyclophos-phamide in steroid resistant idiopathic nephrotic syndrome. J Coll Physicians Surg Pak 2005; 15(6): 329-32.
23. Frassinetti Castelo Branco Camurça Fernandes P, Bezerra Da Silva G Jr, De Sousa Barros FA, Costa Oliveira CM, Kubrusly M, Evangelista JB Jr. Treatment of steroid-resistant nephrotic syndrome with cyclosporine: study of 17 cases and a literature review. J Nephrol 2005; 18(6): 711-20.
24. Iyengar A, Karthik S, Kumar A, Biswas S, Phadke K. Cyclosporine in steroid dependent and resistant childhood nephrotic syndrome. Indian Pediatr 2006; 43(1): 14-9.
25. Martinelli R, Okumura AS, Pereira LJ, Rocha H. Primary focal segmental glomerulosclerosis in children: prognostic factors. Pediatr Nephrol 2001; 16(8): 658-61.
26. Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French Society of Pediatric Nephrology. J Pediatr 1994; 125(6 Pt 1): 981-6..