Saudi J Kidney Dis Transpl 2010;21(3):484-487

Saudi Journal of Kidney Diseases and Transplantation

Original Article

Treatment of Steroid Resistant Nephrotic Syndrome in Children

Jameela A. Kari[1], Manal Halawani[2]

Departments of [1]Pediatrics and [2]Histopathology, King Abdul Aziz University Hospital, Jeddah, Saudi Arabia

ABSTRACT. Achieving remission in children with Steroid-Resistant Nephrotic Syndrome (SRNS) could be difficult. Many immunosuppressive drugs are used with variable success rates. We have studied the response of children with SRNS who presented to our pediatric's renal unit between 2002 and 2007 to various modalities of therapy. We included patients with no response to prednisolone (60 mg/M^2/day) after four weeks of therapy; all the patients had renal biopsy and follow-up duration for at least one year. We excluded patients with congenital nephrotic syndrome, lupus, or sickle cell disease. There were 31 (23 girls and 8 boys with F: M= 2.9:1; the mean age at presentation was 4.2 ±_3.2) children who fulfilled the inclusion criteria. The mean duration of follow up was 3.1 ± 1.6 years. Twenty children (65%) achieved partial (6 children) or complete (14 children) remission. There were 16 children treated with cyclophosphamide either oral or intravenous, and only 4 of them (25%) achieved remission. Seven children received oral chlorambucil, and only2 of them (28.5%) achieved remission; none of the children experienced side effects. Fifteen children received cyclosporine, and only eight of them (53%) achieved remission. Six children developed gum hypertrophy and one had renal impairment, which was reversible after discontinuing the drug. Mycophonelate mofetil (MMF) was used as the last option in 5 children, and 2 of them achieved complete remission. One child developed a systemic cytomegalovirus (CMV) infection which indicated discontinuing the drug. Fourteen (45%) children needed more than one immunosuppressive therapy. Three children progressed to end stage renal failure and required dialysis. We conclude that SRNS in children is a difficult disease with significant morbidity. However, remission is achievable with cyclosporine and other immunosuppressive agents. Treatment should be individualized according to the underlying histopathology, and clinical and social conditions of the children.

Correspondence to:

Prof. Jameela Kari
Pediatrics Department,
King Abdul Aziz University Hospital,
P.O. Box 80215, Jeddah 21589, Saudi Arabia
E-mail: jkari@doctors.org.uk

Introduction

Steroid resistant nephrotic syndrome (SRNS), represents around 10% of childhood idiopathic nephrotic syndrome,[1] and failure to induce remission in them, which is a difficult task, carries a significant risk of progression to end

stage renal failure (ESRF).[2] The underlying histopathology is usually non-minimal change disease (non-MCD) with a high incidence of focal segmental sclerosis (FSGS). Over the past two decades, the incidence of FSGS has increased markedly all over the world including Saudi Arabia.[3-5] FSGS is the most frequent cause of ESRF and constitutes 10% of all children undergoing dialysis.[2] Patients with the collapsing type FSGS and reduced GFR at the start of therapy, have the worst prognosis.[6,7] About 20-30% of patients with classically defined primary FSGS harbor genetic mutations in podocyte-specific genes such as nephrin, podocin, α-actinin-4, and CD2AP[8,9] and those with genetic mutations rarely respond to immunosuppressive therapy.[10]

Children with SRNS may be treated with immunosuppressive agents such as cyclophosphamide, chlorambucil, cyclosporine, or mycophenolate mofetil (MMF), or with non-immunosuppressive agents such as ACE inhibitors. Optimal combinations of these agents with the least toxicity remain to be determined.[11] However, previous studies showed complete or partial remission rates of about 60% in children with SRNS.

In this study we report the response of our patients with SRNS to various modalities of therapy at our institute.

Patients and Methods

We reviewed the charts of all children with SRNS, presented to the renal unit at King Abdulaziz University Hospital (KAUH) between 2002 and 2007.

We included patients with no response to prednisolone (60 mg/M^2/day) after four weeks of therapy; all the patients had renal biopsy and follow-up duration for at least one year. We excluded patients with congenital nephrotic syndrome, lupus or sickle cell disease. We have recorded the age of presentation, duration of follow-up, results of histopathology, modality of treatment, response to therapy, and serum creatinine.

All children were maintained on enalapril and on alternate-day prednisolone, in addition to their immunosuppressive therapy (cyclosporine, alkylating agents or MMF). We commenced children with FSGS on cyclosporine, those with MCD or MCD variants such as IgM nephropathy or mesangioproliferative GN (MesPGN) on cyclophosphamide, and those with membranoproliferative glomerulonephritis on antiplatelets agent (aspirin), in addition to enalapril and alternate-day prednisolone. However, this strategy was not followed strictly since some patients had financial restraints.

Results

Thirty one children fulfilled the inclusion criteria; 23 girls and 8 boys with F: M= 2.9:1; 14 (45%) children were Saudis and the remainder was from variable racial backgrounds (8 Asians, 4 Arabs, 2 Africans and 3 from the Far East). Most of the children were from poor social background and the compliance to medication was not trusted in many of them.

The mean age of the children at presentation was 4.2 ± 3.2 (range 1-12) years, and the mean duration of follow-up was 3.1 ± 1.6 years. Their mean serum albumin at presentation was 15.6 ± 7.1 g/L and all of them had 4+ proteinuria. The mean serum creatinine was 50.4 ± 45.6; 5 children revealed elevated creatinine at presentation. Three children had low complements at presentation and none had positive hepatitis surface antigen or positive antinuclear antibody (ANA). The renal histopathology was compatible with FSGS in 17 (55%) children, IgM nephropathy in 7 (23%) children, MCD in 2 (6%) children, MesPGN in 2 (6%) children, and C1q nephropathy in 3(9%) children.

Twenty (64.5%) children achieved partial (6 (19.3%) children) or complete remission (14 (45.2%) children). There were 14 (45%) children who required more than one immunosuppressive therapy. Three children progressed to ESRF and required dialysis.

There were 16 children treated with either oral or intravenous cyclophosphamide (6 FSGS, 4 IgM, 2 MesPGN, 2 MCD and 2 C1qNP). Only 4 (25%) children (2 FSGS, 1 MCD and 1 IgM) achieved complete remission. Five children were tried on monthly intravenous cyclo-

phosphamide as part of prospective study.[12] Only 3 of them, achieved partial non-sustained remission.

Seven children received oral chlorambucil (5 IgM, 1 FSGS and 1 MesPGN); 2 (28.5%) of them achieved complete remission (both had IgM).[13] None of the children experienced side effects.

There were 15 children who received cyclosporine (9 FSGS, 2 IgM, 2 C1qNP 1 MCD and 1 IgA); 8 (53%) of them (5 FSGS, 1 IgM and 1 IgA) achieved remission. Six children developed gum hypertrophy and one had renal impairment, which was reversible after discontinuing the drug.

MMF was used as the last option in 5 children (3 FSGS, 1 C1qNP and 1 IgM). Two of them achieved complete remission (1 FSGS and 1 IgM). One child developed a systemic cytomegalovirus (CMV) infection, which indicated discontinuing the drug.

Forty five percent (14 children) needed more than one immunosuppressive therapy. Three children progressed to end stage renal failure and required dialysis

Discussion

Our results showed that 45% of children with SRNS achieved complete remission and 19% achieved partial remission, which is comparable to previous reports. The rate of complete remission of SRNS after induction therapy using different immunosuppressive agents is reported to range from 30% to 84%, depending on the treatment schedule and on the underlying defects of FSGS.[2] This is despite the inadequate therapy because of financial and social difficulties. For example, cyclosporine could not be given as the first choice for some children because of their inability to keep appointments for monitoring of the drug levels.

The response rate to the alkylating agents in our study was similar to previous reports. Tarshish et al reported 25% response with cyclophosphamide, which was the same response to prolonged course of prednisolone.[14] Similarly, in the systematic review of 9 randomized clinical trials (RCT), the rate of complete remission was less than 30% with high relapse rate.[15] Moreover, due to unfavorable toxic side effects and variable reported efficacy in the literature, the alkylating agents are not recommended for primary therapy in FSGS.[16]

The best result in our group was achieved by using cyclosporine. This is similar to previous reports that found better remission with cyclosporine than intravenous cyclophosphamide.[17] Similarly, the systematic review of 11 RCT found that treatment of SRNS with cyclosporine was associated with a significant percentage of complete remission.[11]

Prolonged use of cyclosporine in association with prednisolone could result in 75% remission rate.[18] These results suggest that cyclosporine rather than cyclophosphamide should be used as a first line therapy for children with SRNS.[11,17]

We used in MMF as the last resource in 5 children and two achieved complete remission (40%). Ehrich et al reported a 50% response rate to MMF in 44 patients pooled from 12 different publications.[2]

We did not use genetic a study in any of our patients before starting therapy. It useful to screen for genetic mutations as podocin mutations are found in 10-30% of sporadic cases of SRNS with FSGS.[19] Identifying these patients with mutations, may result in avoiding unnecessary exposure to immunosuppressive medications and their side effects.[2,10]

We conclude that SRNS in children is a difficult disease with significant morbidity. However, remission is achievable with cyclosporine and other immunosuppressive agents. Treatment should be individualized according to the underlying histopathology, clinical and socioeconomic condition of the children.

References

1. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change Nephrotic syndrome: Report of the International Study of Kidney Disease in Children. J Am Soc Nephrol 1997;8 (5):769-76.
2. Ehrich JH, Pape L, Schiffer M. Corticosteroid-resistant Nephrotic syndrome with focal and

segmental glomerulosclerosis: An update of treatment options for children. Paediatr Drugs 2008;10(1):9-22.
3. Hogg R, Middleton J, Vehaskari VM. Focal segmental glomerulosclerosis-epidemiology aspects in children and adults. Pediatr Nephrol 2007; 22(2):183-6.
4. Borges FF, Shiraichi L, da Silva MP, Nishimoto EI, Nogueira PC. Is focal segmental glomerulosclerosis increasing in patients with nephrotic syndrome? Pediatr Nephrol 2007;22(9): 1309-13.
5. Kari JA. Changing trends of histopathology in childhood nephrotic syndrome in western Saudi Arabia. Saudi Med J 2002;23(3):317-21.
6. Abeyagunawardena AS, Sebire NJ, Risdon RA, et al. Predictors of long-term outcome of children with idiopathic focal segmental glomerulosclerosis. Pediatr Nephrol 2007;22(2): 215-21.
7. Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: Presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol 2004;15(8):2169-77.
8. Pollak MR. The genetic basis of FSGS and steroid-resistant nephrosis. Semin Nephrol 2003;23(2):141-6.
9. Liapis H. Molecular pathology of nephrotic syndrome in childhood. A contemporary approach to diagnosis. Pediatr Dev Pathol 2008;11(4): 154-63.
10. Ruf RG, Lichtenberger A, Karle SM, et al. Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome. J Am Soc Nephrol 2004; 15(3):722-32.
11. Hodson EM, Habashy D, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst Rev 2006;2:CD003594.
12. Alshaya HO, Al-Maghrabi JA, Kari JA. Intravenous pulse cyclophosphamide, is it effective in children with steroid-resistant nephrotic syndrome? Pediatr Nephrol 2003;18(11):1143-6.
13. Kari JA, Alkushi A, Alshaya HO. Chlorambucil therapy in children with steroidresistant Nephrotic syndrome. Saudi Med J 2006;27 (4):558-9.
14. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol 1996;10 (5):590-3.
15. Habashy D, Hodson EM, Craig JC. Interventions for steroid-resistant nephrotic syndrome: a systematic review. Pediatr Nephrol 2003;18 (9):906-12.
16. Hodson EM, Craig JC. Therapies for steroid-resistant nephrotic syndrome. Pediatr Nephrol 2008;23(9):1391-4.
17. Ehrich JH, Geerlings C, Zivicnjak M, Franke D, Geerlings H, Gellermann J. Steroid-resistant idiopathic childhood nephrosis: overdiagnosed and undertreated. Nephrol Dial Transplant 2007;22(8):2183-93.
18. Niaudet P. Genetic forms of nephrotic syndrome. Pediatr Nephrol 2004;19(12):1313-8.
19. Gipson DS, Gibson K, Gipson PE, Watkins S, Moxey-Mims M. Therapeutic approach to FSGS in children. Pediatr Nephrol 2007;22(1): 28-36.