Original Article

Treatment of Steroid Resistant Nephrotic Syndrome in Children

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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/M²/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 only 2 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. Mycophenolate 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.

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Introduction

Steroid resistant nephrotic syndrome (SRNS), represents around 10% of childhood idiopathic nephrotic syndrome, and failure to induce remission in them, which is a difficult task, carries a significant risk of progression to end stage renal failure.
stage renal failure (ESRF). 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. FSGS is the most frequent cause of ESRF and constitutes 10% of all children undergoing dialysis. Patients with the collapsing type FSGS and reduced GFR at the start of therapy, have the worst prognosis. 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 and those with genetic mutations rarely respond to immunosuppressive therapy.

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. 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/M2/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 anti-platelets 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-
phosphamid as part of prospective study. 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). 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. 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. Similarly, in the systematic review of 9 randomized clinical trials (RCT), the rate of complete remission was less than 30% with high relapse rate. 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.

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. Similarly, the systematic review of 11 RCT found that treatment of SRNS with cyclosporine was associated with a significant percentage of complete remission. Prolonged use of cyclosporine in association with prednisolone could result in 75% remission rate. These results suggest that cyclosporine rather than cyclophosphamide should be used as a first line therapy for children with SRNS.

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.

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. Identifying these patients with mutations, may result in avoiding unnecessary exposure to immunosuppressive medications and their side effects.

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


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