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Long Term Prognosis of Steroid Resistant Nephrotic Syndrome in Children

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Abstract

Background: We aimed to investigate the long-term outcome of children with steroid resistant nephrotic syndrome (SRNS).
Methods: Medical charts of the 88 children who were diagnosed to have SRNS between January 1990 and December 2008 were analyzed retrospectively. We evaluated the response to different immunosuppressive agents and the prognosis of the patients.
Results: 73 of the patients were initially steroid resistant and 15 of them developed steroid resistance during follow up (late steroid resistance). Focal segmental glomerulosclerosis was the most common histopathological type. Cyclophosphamide, Cyclosporine A, Chlorambucile, Tune-Mendosa protocole and Mycophenolate Mofetile were used as immunosuppressive agents. Among patients with initial steroid resistance complete remission was achieved in 37 (61.7 %) patients and partial remission in 11 (18.3 %). Nine (15%) of the patients developed CKD and 3 (5 %) developed ESRD. These patients who developed CKD and ESRD were diagnosed as FSGS histopathologically. Initially 1 patient died because of cerebrovascular attack and 1 died because of peritonitis during continuous ambulatory peritoneal dialysis (CAPD). Twelve (92.6%) of the patients with late steroid resistance achieved complete remission, one of them (7.4 %) developed ESRD and two of them lost to follow up. We did not observe severe side effects that cause termination of treatment.
Conclusion: Treatment of SRNS is still a challenging issue for pediatric nephrologists. Because of the paucity of controlled studies, therapy regimens mostly depend on individual requirements, clinicians' experience and social and financial facilities of the country.

Key Words: Children, Steroid resistant, Nephrotic syndrome, Prognosis

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Introduction

Steroid resistant nephrotic syndrome (SRNS) accounts for approximately 10-20 % of idiopathic nephrotic syndrome cases in childhood (1, 2). The overall prognosis of the disease is poor; with a high proportion of children develop chronic kidney disease (3). The optimal management of SRNS is still challenging and there is no agreement among pediatric nephrologists (4). In this retrospective study we aimed to evaluate the long-term results of treatment strategies administered in children with SRNS and to assess the optimal management to avoid or slow the progression to chronic kidney disease.

Patient and Methods

We retrospectively analyzed medical reports of 88 children who were diagnosed to have SRNS between January 1990 and December 2008. Seventy-three of these patients were initially steroid resistant and fifteen were initially responded to steroids but developed resistance during follow up.

Steroid resistant NS was defined as failing to have remission after 8 weeks of steroid therapy at a dose of 60 mg/m^2/day (maximum 60 mg/day)(5) Late steroid resistance was defined as persistant proteinuria during for or more weeks of corticosteroids following one or more remissions (6). Clinical and laboratory data of these patients were obtained from the hospital charts, and treatment regimens applied to the patients were evaluated. After percutaneous renal needle biopsies were performed, different immunosuppressive agents were administered to the patients. Cyclophosphamide (CPM) was given at a dose of 2 mg/kg/day for 8-12 weeks, chlorambucil (CLM) 0.2 mg/kg/day for 8-12 weeks, cyclosporine A (CsA) 3-5 mg/kg/day for 6-12 months, and mycophenolate mophetil (MMF) 1200 mg/m^2/day together with low dose prednisolone (10 mg/m^2/day). Tune-Mendosa protocole (TMP) was applied to the patients with SRNS who were unresponsive to these agents (Table-1).

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Table 1. Tune Mendosa Protocole

Weeks	IV. Pulse Methylprednisolone (maximum dose:1 gram/day)	Oral Prednisolone (maximum dose 60 mg/day)
1-2	30 mg/kg/1 week	
3-10	30 mg/kg/1 week	1,5mg/kg/Eod
11-18	30 mg/kg/2 weeks	1 mg/kg/ Eod
19-50	30 mg/kg/1 month	0,5mg/kg/ Eod
51-82	30 mg/kg/2 months	0,5mg/kg/ Eod

Eod:every other day

Response to different therapeutic regimens and the long-term prognosis of the patients were evaluated retrospectively.

Remission was defined as reduction of proteinuria to <4 mg/m^2/hour or urine albumin dipstick of negative or trace for 3 consecutive days; partial remission (PR) as improvement of serum albumin levels to normal levels despite persistant proteinuria; chronic kidney disease (CKD) as structural or functional abnormalities of the kidney present for more than 3 months (7). End stage renal disease (ESRD) as GFR <15 ml/min/1.73 m^2 and the need for renal replacement therapy.

Patients were divided into two groups according to their ages; Group 1: patients who were ≤ five years but > 1 year old and Group 2: patients > five years old. These two groups were compared to each other according to their laboratory and clinical data and to the response to different therapeutic regimens. Children under the age of one year were not included in this study.

Statistical Analyses

Mann Whitney-U test, Khi-Square test and Fisher's Exact test were used for statistical analyses and p values below 0.05 ($p<0.05$) were accepted to be significant.

Results

Among 392 patients with idiopathic nephrotic syndrome followed up between 1990 and 2008, 88 patients (22.4%) were diagnosed as steroid resistant. Mean duration of follow up was 8 years and 6 months (2.5 months-18 years). Seventy-three of these patients (19.4 %) were initially steroid resistant and 15 (3.2 %) developed steroid resistance during follow up.

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Results of the Patients With Initial Steroid Resistance

Forty of these patients (54.8 %) were boys and 33 (45.2%) were girls. Forty of the patients (54.2%) were under or at the age of 5 while 33 (45.2%) were above 5 years. Patients under the age of 1 year old were not included in this study.

FSGS was the most common histopathological type of the disease and detected in 70.6 % of the patients, followed by diffuse mesengial proliferation (17.7 %) and minimal change disease (11.7 %). In Group 1, FSGS was detected in 68.4 % of the patients and in Group 2, in 74.2 % of the patients. Three patients were diagnosed as chronic renal disease at admission, 6 patients were lost to follow up; and one patient died because of cerebrovascular accident. Different immunosuppressive treatments were administered to the other 63 patients. Response to Immunosupressive Agents: (Table 2)

Table 2. Response rates to different immunosupressive treatments in initially steroid-resistant patients

Immunosupressive treatment	Number of patients	Complete remission n (%)	Partial remission n (%)	No remission n (%)
Cyclophosphamide	48	24(50 %)	2 (4.2 %)	22(45.8 %)
Chlorambucile	20	5(25 %)	3 (15 %)	12(60%)
Cyclosporine A	10	2(20%)	3(30%)	5(50%)
Tune Mendosa	15	4(26.7%)	2(13.3%)	9(60 %)
Mycophenolate Mophetile	8	2(%25)	1(12.5%)	5(%62.5)

Results of patients with primary steroid resistance

Cyclophosphamide (CPM):

Cyclophosphamide was the first drug administered to 53 patients. Five patients were lost to follow up. 24 (50 %) of the rest achieved complete remission and 2 (4.2 %) partial remission. 22 patients (45.8 %) were unresponsive to CPM treatment. Among the patients who were unresponsive to CPM, 1 patient developed CKD, 2 were treated with TMP, 2 with MMF, 2 with CsA and 13 with CLM. Two of the patients who were unresponsive to CPM were lost to follow up (Figure 1).

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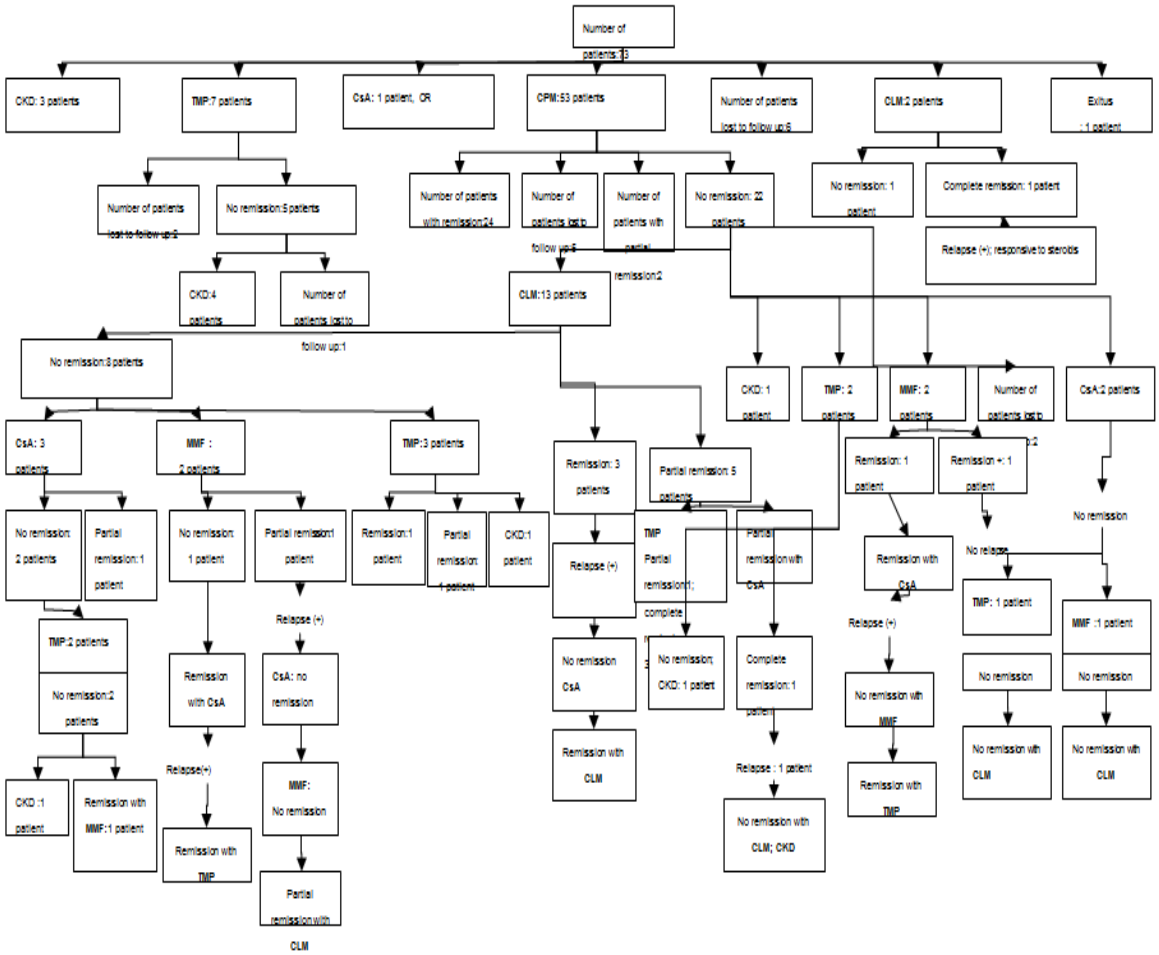

Figure 1. Two of the patients who were unresponsive to CPM were lost to follow up

Chlorambucile(CLM):

Initially two patients were treated with CLM and one of them responded to the treatment while the other did not. Thirteen patients who were unresponsive to CPM were treated with CLM and 3 of them achieved complete remission and 2 partial remission. 8 of the 13 patients were unresponsive to CLM. Five other patients unresponsive to several immunosuppressives were also given CLM and only one of them

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had remission while one other had PR (Figure 1).

Cyclosporine A (CsA):
One patient who was initially treated with CsA achieved partial remission. CsA was also given to 2 patients who were unresponsive to CPM but none of them achieved remission. Three patients who were unresponsive to both CPM and CLM were treated with CsA and one of them achieved partial remission but two were also unresponsive to CsA. Two patients who were unresponsive to CPM, CLM and MMF were treated with CsA, one of them achieved remission and the other one was unresponsive. The patient who achieved remission had relapses during follow up and entered remission with TMP. One patient who was unresponsive to CPM and partially responsive to CLM was treated with CsA and achieved partial remission. One patient who was unresponsive to both CPM and MMF achieved remission with CsA (Figure 1).

Tune-Mendosa protocole (TMP):
TMP was administered initially to seven patients. Two of them were lost to follow up and the reminder 5 did not respond to treatment. Four of the five patients developed CKD and one of them was lost to follow up. TMP was also administered to patients who were unresponsive to other immunosuppressive agents. Four of these patients achieved complete remission and two patients achieved partial remission while four were unresponsive to treatment (Figure 1).

Mycophenolate Mophetile (MMF):
MMF was administered to 8 patients in our study period. Three of these patients were unresponsive to CPM, one was unresponsive to CsA and CPM, three to CPM, CLM and CsA, and one to all other immunosupressives used. After therapy with MMF, 2 patients achieved complete and one partial remission, but five had no response (Figure 1) .

Results of The Patients With Late Steroid Resistance
Fifteen of the patients who initially responded to steroid treatment developed steroid resistance during relapses. Two of them lost to follow up. One patient was treated with CLM and responded to treatment. Twelve of the patients were treated with CPM and 9 of them achieved remission. Two of the patients who were unresponsive to CPM were treated with CsA and achieved remission. The other patient was treated with MMF but no remission was achieved. Prognosis of the patients with late steroid resistance is

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summarized in Figure 2 and the overall prognosis of the patients with initial and late steroid resistant is summarized in Table 3.

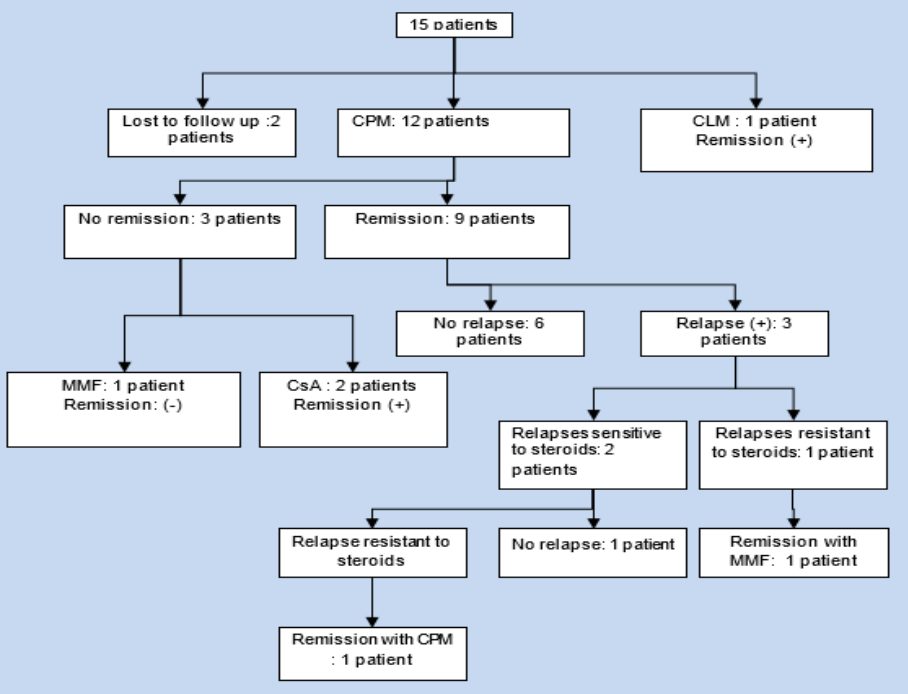

Figure 2: Prognosis of patients with late steroid resistance CPM: Cyclophosphamide, CLM:Chlorambucile, CsA: Cyclosporine, MMF: Mycophenolate mophetile

Table 3. Overall prognosis of the patients with SRNS

	Patients with LSR		Patients with ISR	
	n	%	n	%
Complete remission	12	92.6	37	61.7
Partial remission	0	0	11	18.3
CKD	0	0	9	15
ESRD	1	7.4	3	5

CKD: Chronic Kidney Disease; ESRD: End stage renal disease; ISR: Initial steroid resistance; LSR; Late steroid resistance; SRNS: Steroid resistant nephrotic syndrome

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Discussion

The rate of steroid resistance in children with nephrotic syndrome is increasing with time. Banaszak and Banaszak (8) demonstrated a significant increase in primary steroid resistance in the latter decade. It was reported to be 31.4% in children followed up between 1996 and 2005 while it was 15.8 % between 1986 and 1995. This increasing ratio is important because SRNS is responsible for the increasing risk of end stage renal disease (ESRD) leading to a 34-64 % of probability of developing ESRD in 10 years (4). In our study primary steroid resistance was detected in 73 of 392 patients with INS (19.6 %). It is suitable with the results of Banaszak's study since our study includes the patients between 1990 and 2008.

In the study of ISKDC in 1981 MCD, FSGS and DMP each accounted for about a quarter of children with SRNS (9). But in recent reports there is growing evidence that FSGS forms the majority of the histopathological lesions of biopsy specimens in children with SRNS (10). In the study of Gulati et al (11) FSGS was the commonest lesion accounting for 59 % of patients. Zagury et al (4) detected FSGS in 70 (54.4%) of their patients. Although the overall rate was different from these studies Banaszak and Banaszak (8) reported an increasing rate of FSGS in their patients in the last decade (17.9 % between 1985-1995 vs 20.4 % between 1996 and 2005). In concordance with these studies FSGS was also the most frequent histopathological lesion in our study but with higher frequency detected in 70.6 % of patients. FSGS was also more commonly observed in older children. ISKDC (9) reported the mean age for FSGS to be 6 years old and Sorof (12) et al detected that MCD decreased and FSGS increased by age. Steroid resistance in nephrotic syndrome is the major risk for chronic kidney disease (13) and FSGS is the commonest histopathological pattern and also the major cause of CKD and ESRD (14, 15). CKD develops in 23 % and ESRD develops in 21 % of children with FSGS following the five year after diagnosis. In our study among patients with histopathologically diagnosed as FSGS, 22 % of the children developed CKD, and 8.3 % developed ESRD.

Although the prognosis is poor the best treatment of SRNS is still challenging for pediatric nephrologists. In the recent report of KDIGO calcineurin inhibitors (CNI) is recommended as the first line treatment and they do not recommend alkylating agents (16). But more previous reports obtained a success rate as much as 80 % with intravenous CPM (17). Abeyagunawardena reported a remission rate of 43 % with cyclophosphamide in their study in 2007 (18). They administered monthly pulses of CPM and they did not observe severe side effects. In the study of Gulati et al (19) they also administered IV cyclophosphamide to 20 patients with SRNS and 13 (65 %) of these patients reached complete remission and they reported the mean duration of remission following last dose of cyclophosphamide in these

children to be 12.5 +/- 11.9 months. They did not observe severe side effects in this study accept transient nausea and vomiting during infusion in two patients and alopecia in one patient. Our study population mostly included the patients treated prior to the recommendations of KDIGO and oral cyclophosphamide was generally the first choice of treatment in our clinics at that time. Remission was achieved in 50 % of patients who were initially steroid resistant and 69.2% of patients with late steroid resistance. These results were in concordance with previous reports despite oral therapy. No severe side effects have been observed during treatment in our study as well.

Although CPM is more often used, CLM has also been used in the treatment of SRNS (20). However the response rates are lower with CLM. Niaudet et al (3) administered CLM in 74 patients with SRNS and only 14 of them achieved complete and partial remission. We used CLM in children with CPM resistance; 25 % of children achieved complete and 15 % partial remission. 25 % of patients had relapses during follow up.

Since 1986 CsA has been used in SRNS and it is the recommended therapy in the recent guidelines of KDIGO (16). CsA reduces proteinuria both by immunological mechanisms and stabilization of actin cytoskeleton in kidney podocytes (21). In the study of Hamasaki et al (22) 6 of 7 children (85.7 %) with FSGS who were treated for 12 months with CsA achieved complete remission. In the randomized, multi-centered study of Plank et al (23) CsA was detected to be more effective at least achieving partial remission; 60 % of the patients entered complete or partial remission with CsA whereas only 17 % of children do with CPM. Ehrich et al (24) reported a higher remission rate as 77 % in their study with idiopathic FSGS group; they combined CsA and oral prednisolone treatment with intravenous pulses of methyl prednisolone. In our study CsA was administered to a small number of patients with a low remission rate of 20 %. However 8 of 10 patients were also unresponsive to other immunosuppressive agents. Therefore this low remission rate of CsA therapy may be attributable to the selection of patients with more intractable disease pattern.

Although there are few studies with mycophenolate mophetile, the results of response rates may be encouraging. In a previous study by Montane (24); MMF was administered with angiotensin converting enzyme receptor blockage and the authors detected decrease in proteinuria levels. In more recent studies remission rates as 67 % (26) and 61 (27) were reported with MMF. Mekahli et al (28) used MMF in children who were CsA dependent and they observed that withdrawal of oral steroids and CsA was achieved with MMF. We administered MMF to 6 patients in our study. Complete remission was achieved in 2 of them and partial remission was achieved in one suggesting that MMF may be effective

to control the disease at least in short term and with less side effects.

Methyl prednisolone pulses have been used in SRNS for many years. The first treatment regimen is suggested in 1990 by Tune and Mendosa (29). They observed a complete remission in 22 of 32 (65.6%) children with FSGS with this protocole; 3 children (9.4 %) had mild, 2 (6.2 %) had moderate protenuria and nephrotic range proteinuria was observed in 6 (19 %) of these patients (30). The following studies similar to Tune and Mendosa protocole revealed remission rates as 38-82 % (31, 32) . Pena et al (33) administered IV pulse methyl prednisolone to all of the 30 children and CPH to 24 of them and they reported a complete remission rate of 73 %; partial remission rate of 10 %. Five of the patients (16.6 %) in this study did not respond to treatment and 2 of these nonresponders developed ESRD. Authors concluded that IV pulse methyl prednisolone can be an effective alternative treatment both isolated or with subsequent CPH treatment (33). Although the remission rates are reported to be high, many pediatric nephrologists are anxious about the side effects of long-term steroid therapy.

In conclusion, treatment of steroid-resistant nephrotic syndrome is still controversial. Response to various immunosuppressive treatments may differ individually and vary over time. New guidelines are prepared based on experts' opinion and evidence, but because of the lack of controlled studies it is tought that these guidelines may sometimes complicate management of these patients. Therapy regimen must therefore be determined according to the clinician's experience, individual requirements, and social and financial facilities of the country.

Conflict of interest:None declared.

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