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Treatment Strategies for Childhood Steroid-Resistant Nephrotic Syndrome

Hala Salah El-Din Talaat[1], Samar Sabry[1], Mohammed Farouk Mohammed[1*] and Ashraf Ayad[2]

[1]Pediatrics Department, Faculty of Medicine, Cairo University, Egypt.
[2]Ministry of Health and Population, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Author HSET designed the study. Author SS wrote the protocol, and wrote the first draft of the manuscript. Author MFM performed the statistical analysis, and managed the analyses of the study, and author AA collected and tabulated the data and managed the literature searches. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Background: Nephrotic syndrome (NS) is a common childhood kidney disease caused by impaired glomerular function, characterized by protein leakage from the blood to the urine through the glomeruli, resulting in proteinuria, hypoalbuminemia, hypercholesterolemia and generalized edema. NS is descriptively classified upon the patients' response to steroid treatment as steroid-sensitive NS (SSNS) or steroid-resistant NS (SRNS).
Aim: describe and compare different management strategies for SRNS.
Methods: This retrospective study included 53 SRNS who were attending the Nephrology Outpatient Clinic, Children's Hospital, and Cairo University for follow-up.
Results: out of 53 SRNS patients, 29 (54.72%) patients showed complete response to immunosuppressive therapy, while 14 (25.42%) showed partial response and the remaining 10 (18.87%) showed no response.
Conclusion: Partial response to steroids or to first line of immunosuppressive therapy predicts better response to further immunosuppressives in SRNS patient. Cyclophosphamide is a preferable line in MCNS as it gives good results (50% complete response) with the advantage of lower cost and shorter duration of use. In patients with

**Corresponding author: Email: m.farouk76@yahoo.com;*

non-minimal change lesions or those who failed to respond to cyclophosphamide, cyclosporine is used.

Keywords: Nephrotic syndrome; steroid-sensitive nephrotic syndrome; steroid-resistant nephrotic syndrome; children.

1. INTRODUCTION

Nephrotic syndrome (NS) is a common childhood kidney disease caused by impaired glomerular function, characterized by protein leakage from the blood to the urine through the glomeruli, resulting in proteinuria, hypoalbuminemia, hypercholesterolemia and generalized edema [1]. Most children with NS have idiopathic NS, rather than NS secondary to an immune complex glomerulonephritis. The most common causes of idiopathic NS in children are minimal change NS (MCNS) and focal segmental glomerulosclerosis (FSGS) [2]. NS is descriptively classified upon the patients' response to steroid treatment as steroid-sensitive NS (SSNS) or steroid-resistant NS (SRNS). Podocin mutations (NPHS2 gene) are mostly responsible for SRNS of childhood onset [3]. Management of SRNS is difficult, most patients failing to achieve remission show progressive renal damage [4]. The aim of this study was to compare the efficacy of different management strategies for SRNS.

2. METHODOLOGY

This is a retrospective cohort study from a single center in which records of 53 pediatric SRNS patients who were following at the Nephrology Clinic, Children's Hospital - Cairo University, were retrospectively reviewed. NS patients in our clinic were guided to follow-up on either Monday or Thursday on random basis. All SRNS patients with age of onset of the disease <16 years following on Monday from January 2002 until December 2011 (10 year-period) were included. Patients with secondary NS, congenital nephrosis, inadequate data in the records, and patients dropping out during follow-up were excluded.

The Scientific Research Committee of Pediatrics Department, Faculty of Medicine-Cairo University, approved the study design. All data were confidential for the research use only.

All patients received oral prednisone or prednisolone at a dose of 2mg/kg/day with a maximum of 60 mg/day. Treatment was continued for 4 weeks and treatment was continued for total of 6 weeks if remission did not occur after 4 weeks. Treatment was continued for 8 weeks in occasional patients in whom non compliance to treatment was suspected.

Patients' data were recorded including demographic data (age of onset, duration of the disease, height, weight and their percentiles), results of renal biopsy, occurrence of complications, and treatment regimens used; for each: order of use, duration, side effects, response assessed by mean protein/creatinine ratio, serum albumin and serum creatinine before and after treatment.

In our unit, cyclophosphamide had been the first line therapy of SRNS due to higher cost of cyclosporine but in recent years, due to the availability of cyclosporine by the health insurance system; it became the first line therapy in patients with FSGS. Cyclophosphamide is given orally at a dose of 2 mg/kg for 3 months or 3mg/kg for 2 months during which steroids were given at a dose of 2mg/k alternate day therapy. Cyclosporine is given at a dose of 5-7mg/kg/day. Cyclosporine level was not done routinely except in those with

insufficient response in a preliminary step to increase the dose or in case of decline of GFR. During cyclosporine therapy steroids were slowly withdrawn to the minimal dose below which proteinuria starts to increase. MMF is given at a dose of 600mg/m^2 with gradual tapering of steroids to the lower possible dose.

Data were statistically described in terms of range, mean±SD, frequencies and percentages. Comparison of quantitative variables between the study groups was done using Student's t test. For comparing categorical data, Chi-square test was performed. A probability value (p value) of <0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel® 2007 (Microsoft® Corporation, NY, USA) and SPSS® (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft® Windows®.

3. RESULTS

Demographic data of patients are shown in Table 1.

Table 1. Demographic data of patients

Item	Patients (n=53)
Age (yrs), mean ± SD	8.60 ± 4.41
median (range)	8 (1.9 – 19)
Age of onset (yrs), mean±SD	4.68 ± 3.11
median (range)	3 (1 - 12)
Duration of follow up (yrs), mean ± SD	3.89 ± 2.36
median (range)	4 (0.5-9)
Male/Female	31/22
Consanguinity, n (%)	5 (9.43%)
Positive family history**, n (%)	6 (11.32%)
Weight (kg), mean ± SD	28.77 ± 13.35
median (range)	26 (10 - 76)
Weight percentile, mean ± SD	43.35±34.46
median (range)	30 (3-97)
Height (cm), mean ± SD	117.74±20.87
Height percentile, mean ± SD	12.06±11.71
median (range)	5 (5-50)
BMI (kg/m^2), mean ± SD	20.64 ± 4.20
HTN*** at presentation, n (%)	9 (16.98%)
CKD 3-5, n (%)	8 (15.09%)

SRNS: steroid resistant nephrotic syndrome, BMI: body mass index, HTN: hypertension, CRI: chronic renal insufficiency.

**P-value less than 0.05 is considered statistically significant.*

*** SRNS in siblings or cousins.*

**** Blood pressure above 95th percentile for age and sex*.

Out of 53 SRNS patients, 47 had performed renal biopsy. Those who did not perform were because of parental refusal. Mesangioproliferative glomerulonephritis (MesPGN) was the most common pathological features and was noted in 20/47 (42.55%) patients, followed by

FSGS, MCNS, and Membranous glomerulonephritis (Membranous-GN), and were noted in 12/47 (25.53%), 10/47 (21.28%), and 5/47 (10.46%) patients respectively. Two SSNS patients had performed renal biopsy because of older age at presentation (>12 years) and reveled MesPGN in both. Most patients performed only light microscopy (LM) as immunoflorescence (IF) and electron microscopy (EM) are not supported by the insurance system. No patients were diagnosed as SLE by other SLE criteria or serology.

Progression of CKD stage according to the National Kidney Foundation's Kidney Disease outcomes Quality Initiative (K/DOQI) [5] from stage 1 is common in SRNS patients. Six of our patients (11.32%) reached stage 5 CKD (end stage renal failure) that necessitated renal replacement therapy, 2 had CKD stage 3 and 4 patients had CKD stage 2. GFR of the patients was measured using Schwartz formula [6].

3.1 Treatment Regimes Used in SRNS

One immunosuppressant was used in 23/53 (43.40%) patients, 2 immunosuppressants were used in 24/53 (45.28%) patients, and 3 immunosuppressants were used in 6/53 (11.32%) patients.

First line of therapy was cyclophosphamide in 44 (83.02%) patients, cyclosporine in 6 (11.32%) patients, mycophenolate moeftil (MMF) in 1 (1.89%) patients and chlorambucil (part of Italian protocol) in 2 (3.77%) patients. Second line of therapy was cyclophosphamide in 1 (1.89%) patient, cyclosporine in 27 patients (50.94%) and MMF in 2 (3.77%) patients. Chlorambucil was used (part of Italian protocol) as first line in 2 patients (3.77%).

3.2 Response to Immunosuppressants

Total number of patients who showed complete response to immunosuppressives was 29/53 (54.72%) patients (19 became infrequent relapsers and 10 became SDNS), while 14 (25.42%) patients showed partial response (reduction of proteinuria >50% of pre-treatment levels with serum albumin ≥2.5mg/dl) and the remaining 10 (18.87%) patients showed no response.

In order to identify factors that might be related to the response to immunosuppressive therapy, we compared SRNS patients who showed complete response (infrequent relapsers and those who became SDNS), with those who showed no or partial response to therapy. A positive family history of renal disease, a higher initial Pr/C ratio before therapy and lack of partial response to steroids may be related to poor or no response to immunosuppressive therapy *(P<0.05)* (Table 2).

Regarding the effect of therapy on the anthropometric parameters (weight and height), SRNS patients who showed no or partial response to therapy had a significantly lower weight and height percentiles compared to those who showed complete response (P = 0.002 and 0.02 respectively) (Table 3).

Table 2. Factors affecting response to immunosuppressive therapy

Item	Complete response (infrequent relapser & SDNS) (n = 29)	No or partial [a] response (n=24)	*P – value*
Age of onset (yrs), mean±SD	4.55 ± 3.02	4.85 ± 3.28	0.74
median (range)	3 (1 – 11)	1.3 (3.5 - 12)	
Male/Female	20 / 9	11 / 13	0.10
Consanguinity, n (%)	1 (3.45%)	4 (16.67%)	0.16
Family history, n (%)	0 (0.00)	6 (25%) [b]	0.00*
HTN at presentation, n (%)	3 (10.34%)	7 (29.17%)	0.16
Initial urinary Pr/C ratio (mg/g)	6.61 ± 2.86	9.55 ± 4.15	0.00*
mean ± SD (range)	(3 – 13)	(3.5 – 20)	
Initial serum albumin (g/dl), mean ± SD	1.56 ± 0.54	1.33 ± 0.37	0.09
Initial serum creatinine, (mg/dl), mean ± SD	0.39 ± 0.14	0.40 ± 0.21	0.84
Partial response to steroid, n (%)	18 (62.07%)	5 (20.83%)	0.00*

*SDNS: steroid dependent nephrotic syndrome, HTN: hypertension, Pr / C ratio: protein to creatinine ratio. *P-value less than 0.05 is considered statistically significant.*

[a] *We preferred to add patients with partial response to those who did not response rather than those who responded completely as some patient with partial response developed chronic renal insufficiency.*

[b] *Out of theses 6 cases, positive family history of renal disease in other siblings were noted in 3 cases and of other relatives in another 3 cases.*

Table 3. Effect of resistance to treatment on anthropometric parameters

Item	Complete response (n=29)	Partial or no response (n=24)	*P – value*
Weight (kg), mean ± SD	30.86 ± 14.36	26.25 ± 11.81	0.21
median (range)	28 (12 – 76)	24 (10 – 54)	
Weight percentile, mean ± SD	56.29±32.04	27.71±31.12	0.002*
median (range)	60 (7-97)	15 (3-95)	
Height (cm), mean ± SD	119.66 ± 21.09	115.42 ± 20.81	0.47
Height percentile, mean ± SD	15.41±13.20	8±8.12	0.02*
median (range)	10 (5-50)	5 (5-40)	
BMI (kg/m^2), mean ± SD	21.32 ± 4.72	19.81 ± 4.06	0.19

BMI: body mass index

**P-value less than 0.05 is considered statistically significant.*

3.3 Response to Individual Immunosuppressant

3.3.1 Cyclophosphamide

Cyclophosphamide was used as the first line of therapy in 44 patients, out of them, 14 patients (31.82%) showed complete response, 18 patients (40.91%) showed partial response, while 12 patients (27.27%) did not show any response.

Thirty-eight biopsies were performed in this group, and according to the results of the pathological examination, 10/38 patients (26.32%) were MCNS, while 28/38 patients (73.68%) were non–MCNS. A complete response to cyclophosphamide therapy was reported in significant number of MCNS patients with than non–MCNS patients (p=0.03) (Table 4).

Table 4. Clinical response in relation to renal biopsy results in SRNS patients received cyclophosphamide as the 1st line therapy

Item	MCNS (n=10)	Non – MCNS (n=28)	*P – value*
Complete response, n (%)	5 (50%)	4 (14.29%)	0.03*
Partial response	4 (40%)	13 (46.43%)	
No response	1 (10%)	11	

MCNS: minimal change nephritic syndrome
**P-value less than 0.05 are considered statistically significant.*

Of the six patients who did not perform biopsy, 5 showed complete response and one showed partial response to therapy. Of the 30 patients who showed partial or no response, 27 received further immunosuppression (in the remaining 3 patients, either parents refused to continue immunosupression or patients were still on follow-up).

3.3.2 Cyclosporine

Cyclosporine was used as second line therapy after cyclophosphamide in 26 patients and after MMF in one patient. Out of 26 patients, 7 showed complete response, 12 showed partial response and 7 showed no response. All the 7 patients who showed complete response have already showed partial response to cyclophosphamide and all the 7 patients who showed no response showed also no response to cyclophosaphamide (Table 5).

Cyclosporine was used as first line therapy in 6 non–MCNS patients, 3 of them showed complete response (50%) and 3 showed no response (50%).

3.3.3 MMF

MMF was used in 8 patients, as first line therapy in one patient (who showed no response), as 2nd line therapy after cyclosporine in 2 patients, and as 3rd line therapy after cyclophosphamide and cyclosporine in 5 patients. Of the later 7 patients, MMF did not show any additional effect following the other immunosuppressants in 5 patients, showed partial improvement in one patient and leaded to complete response in one patient who failed to show any response to both cyclophosphamide and cyclosporine.

Table 5 compares mean Pr/C ratio in urine, mean serum albumin, and mean serum creatinine levels before and after therapy. A significant improvement was noted in the urinary Pr/C ratio, mean serum albumin after prednisone therapy, also after initiation of the first and second lines of immunosuppressive therapy, but values did not show significant change after the 3rd line of therapy. Changes in the mean values of serum creatinine before and after therapy were not significant except for the mean initial value of patients who received the second line in comparison to the mean value after giving the second line therapy *(P<0.01)*.

The responses of the SRNS patients to treatment after each line of immunosuppressive therapy is shown in Fig. 1.

Table 5. Comparison between protein to creatinine ratio in urine, serum albumin, and serum creatinine levels before and after therapy

(A) Before and after prednisone therapy (n=53)			
Item	***Initial (before treatment)***	***After***	***P-value***
Urinary Pr/C ratio (mg/g)			
– mean ± SD	4.94 ± 3.67	4.89 ± 3.67	0.00*
– median (range)	6.35 (3–20)	3.60 (0.2 – 20)	
Serum albumin (g/dl), mean ± SD	1.45 ± 0.48	2.01 ± 0.53	0.00*
Serum creatinine (mg/dl), mean ± SD	0.39 ± 0.18	0.43 ± 0.18	0.30

(B) Before and after first line therapy (n=53)					
Item	***Initial (1)***	***Before 1st line (2)***	***After 1st line (3)***	***P-value 1 v 3***	***2 v 3***
Urinary Pr/C ratio (mg/g)				0.00*	0.00*
– mean ± SD	4.94 ± 3.67	4.89 ± 3.67	2.32 ± 2.91		
– median (range)	6.35 (3–20)	3.60 (0.2-20)	1.30 (0.01-14)		
Serum albumin (g/dl), mean ± SD	1.45 ± 0.48	2.01 ± 0.53	3.06 ± 0.98	0.00*	0.00*
Serum creatinine (mg/dl), mean ± SD	0.39 ± 0.18	0.43 ± 0.18	0.50 ± 0.39	0.07	0.22

(C) Before and after second line therapy (n=30)					
Item	***Initial (1)***	***Before 2nd line(2)***	***After 2nd line (3)***	***P-value 1 v 3***	***2 v 3***
Urinary Pr/C ratio (mg/g)				0.00*	0.02*
– mean ± SD	8.19 ± 3.90	3.66 ± 3.13	2.01 ± 2.42		
– median (range)	6.85 (3.5-20)	3.20 (0.2-14)	0.95 (0.01-9.2)		
S. albumin (g/dl), mean ±SD	1.40 ± 0.41	2.42 ± 0.73	2.92 ± 0.78	0.00*	0.01*
S. creatinine (mg/dl), mean ± SD	0.39 ± 0.18	0.54 ± 0.45	0.67 ± 0.44	0.00*	0.27

(D) Before and after third line therapy (n=6)					
Item	***Initial (1)***	***Before 3rd line (2)***	***After 3rd line (3)***	***P-value 1 v 3***	***2 v 3***
Urinary Pr/C ratio (mg/g)				0.16	0.4
– mean ± SD	6.85 ± 2.39	1.95 ± 3.13	3.63 ± 4.56		
– median (range)	6.2 (4.2-10.2)	1.95 (0.6–4.30)	1.85 (0.1–11.9)		
Serum albumin (g/dl), mean ± SD	1.25 ± 0.16	2.38 ± 0.65	3.10 ± 0.85	0.00*	0.13
Serum creatinine (mg/dl), mean ± SD (range)	0.38 ± 0.18 (0.2 – 0.6)	0.62 ± 0.23 (0.4 – 1)	2.93 ± 3.56 (0.4 – 8)	0.11	0.14

Pr/C ratio: protein to creatinine ratio

**P-value less than 0.05 is considered statistically significant.*

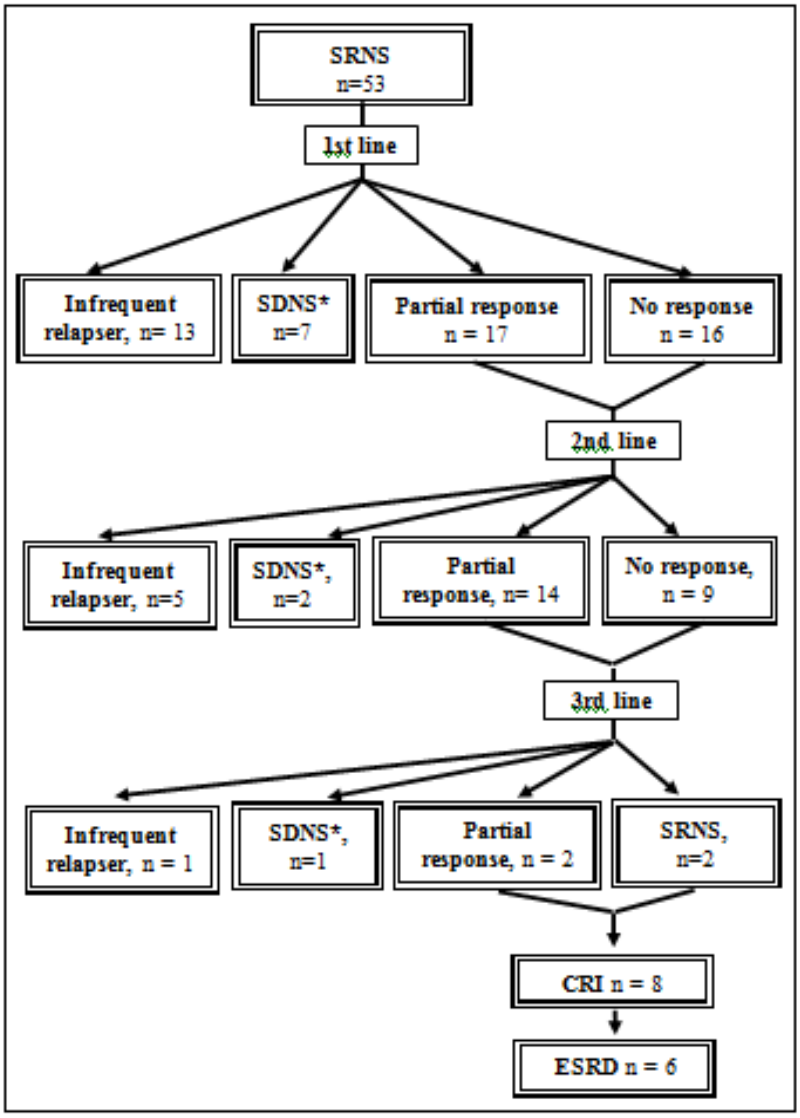

Fig. 1. Course of steroid resistant nephrotic syndrome patients

SRNS: steroid resistant nephrotic syndrome, SDNS: steroid dependant nephrotic syndrome, CRI: chronic renal insufficiency, ESRD: end stage renal disease.
- There is less numbers of SRNS patients with no or partial response after each stage of therapy as some patients entered into CRI before continuing therapy, some parents refused further immunosuppressives and some were still on follow up.
** SDNS patients received Further Immunosuppressive therapy but results are not mentioned.*

4. DISCUSSION

NS is a set of clinical symptoms proteinuria (in children, a protein excretion greater than 40 mg/m^2/hr indicates nephrotic syndrome), hypoproteinemia, edema, and hyperlipidemia [7].

Childhood NS is often steroid sensitive, usually with favorable long-term prognosis characterized by a relapsing course in 50-80% of cases [8]. However, a major problem in the management of children who have frequent relapses is the serious side effects resulting from continuous steroid therapy [9].

A positive family history of renal disease that was recorded in 6 patients, all of them were SRNS. Mutations in the genes encoding various podocyte proteins, including podocin (NPHS2) and nephrin (NPHS1), had been described in a variable proportion of patients with familial and sporadic SRNS [14]. The likelihood of detecting a mutation is higher in patients with family history of NS or its onset in infancy [3].

In our study, the height was clearly affected as evidenced by the low median height percentile (5, with range from 5-50). Major causes of growth retardation in patients with NS are the loss of insulin-like growth factors (IGFs) and/or IGF-binding proteins (IGFBPs) and corticosteroids therapy [15, 16]. Reports suggested that there are changes in serum level of IGFs and IGFBPs among nephrotic children [17,18]. Corticosteroids induce overt elevation of serum IGF-1 levels, which result in the potential development of IGF resistance, one of the main factors responsible for persistent growth retardation [19].

The underlying histopathology in SRNS is usually non-minimal change disease with a high incidence of FSGS [20-22]. FSGS was the most common histopathology among SRNS children in many reports [11,12,23,24]. However, in our study, MesPGN was the most common histopathology in SRNS patients and was noted in 42.55% of them. FSGS, MCNS, and membranous GN were also detected in 25.53%, 21.28%, and 10.64% of patients, respectively.

Similarly Cucer et al [25] noted that MesPGN was the most common histopathology (43.1% of patients). Other histological findings were MCNS, MGN, FSGS and MPGN (17.6%, 15.7%, 7.8% and 7.8% of patients respectively). Nikibakhsh et al [26] also reported that FSGS was not the most prevalent histopathology among their SRNS patients; they reported that the histological findings of their 37 SRNS children included MCNS in 16 patients, MesPGN in 11 patients and FSGS in 10 patients. To some extent, age predicts the histological lesion associated with NS. Children diagnosed before the age of 6 years represented 79.6% of those with MCNS compared with 50% of those with FSGS and only 2.6% of those with MPGN [27].

In our study, the median age of onset MCNS-associated SRNS patients was 3 (range 1-8) years, which was lower than that of SRNS patients with non-MCNS (median 4; range 1-12) years. The mean age at onset of idiopathic SRNS appears to be a function of glomerular morphologic lesion as children with minimal change disease-associated SRNS tend to be younger (2.2-5.1 years) [2,28,29] than those with non-minimal change disease-associated SRNS who are older (6.2-8.72 years) [13,26,30].

Various medications had been used to treat children with SRNS including cyclosporine, MMF, cyclophosphamide, and azathioprine. The rate of complete remission after using different immunosuppressive agents varies from 30% to 84%, depending on the treatment protocols [11,31,32].

In our study, cyclophosphamide, cyclosporine, MMF, and chlorambucil were used for management of SRNS patients. Our results showed that 54.72% of patients showed complete response to immunosuppressive therapy, while 25.42% of patients showed partial response and the remaining 18.87% showed no response. Of SRNS patients, 8/53 (15.09%) developed impairment of kidney functions; 6/53 (11.23%) of them reached ESRD that necessitated renal

replacement therapy. FSGS was the most common histopathology in patients who developed chronic renal insufficiency and was noted in 5 patients, followed by MesPGN in 2 patients and membranous GN in 1 patient. Patients with SRNS are at major risk of developing ESRD, which is seen in <3% of patients with idiopathic NS who respond to glucocorticoid therapy [33]. FSGS is the most frequent cause of ESRD and constitute 10% of all children undergoing dialysis [34].

In our study, cyclophosphamide was the most frequently used medication and was given as first line therapy in 44 patients, 31.82% of them showed a complete response. Thirty-eight biopsies were performed in this group, and accordingly 10/38 patients (26.32%) were MCNS, while 28/38 patients (73.68%) were non-MCNS. A complete response to cyclophosphamide therapy was reported in significant number of MCNS patients than non–MCNS patients, which could indicate that renal pathology may predict the response to cyclophosphamide in SRNS patients.

Similarly, Cucer et al. [25] retrospectively studied the effectiveness of cyclophosphamide in SRNS children and observed a complete remission in 43.1% of patients; remission was also observed mainly in children with MCNS. However, Kari and Halawani [11], noted that out of 16 children who were treated with cyclophosphamide either oral or intravenous, only 4 (25%) achieved complete remission (2 FSGS, one MCNS and one IgM nephropathy).

In our study, cyclosporine was used as first line of therapy in 6 patients, 3 of them showed complete response (50%) and 3 showed no response (50%); all 6 patients were non – MCNS. Cyclosporine was also used as a second line therapy after cyclophosphamide in 26 patients and after MMF in only one patient. Out of these 26 patients, 7 showed complete response, 12 showed partial response and 7 showed no response.

Nearly similar to these results were reported by Nikibakhsh et al [26]. Thirty-seven children with SRNS were treated with cyclosporine for six months, out of them 12 patients (32.4%) went into complete remission, and 2 patients (5.4%) got partial remission. The highest response rate to cyclosporine was observed in patients with MCNS. Tahar and Rachid [12] reported complete remission in 50%, partial remission in 30%, and no response in 20% of their patients. Mello et al [35] also reported complete remission in 53%, incomplete or partial remission in 30% and no improvement in 17% of their patients.

5. CONCLUSION

Partial response to steroids or to first line of immunosuppressives predicts better response to further immunosuppressives in SRNS patient. Most SRNS patients who respond to immunosuppressives show this response after the first or second line therapy.

Cyclophosphamide is a preferable line in MCNS as it gives good results (50% complete response) with the advantage of lower cost and shorter duration of use. In patients with non-minimal change lesions or those who failed to respond to cyclophosphamide, cyclosporine is used.

CONSENT

Consent was obtained from every parent/surrogate of the study candidates. If they had questions, a study physician would clarify the consent form from a standardized set of key

points that covered each section. Parents who indicated that they understood and agreed to the terms of the study provided the consent.

ETHICAL APPROVAL

The Scientific Research Committee of Pediatrics Department, Faculty of Medicine-Cairo University, approved the study design. Data confidentiality was preserved according to the Revised Helsinki Declaration of Bioethics.

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Self-funded by authors. All authors have revised and approved this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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