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Children with Steroid-Resistant Nephrotic Syndrome: A Single -Center Experience

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ABSTRACT

Background: Nephrotic syndrome (NS) is one of the most frequent glomerular diseases among children. While most of the children with primary NS respond to steroid treatment, 10 to 20% of the patients are steroid-resistant, and the best therapy for such cases has never been defined. **Objective:** The present study aimed to evaluate steroid-resistant nephrotic syndrome (SRNS) patients. **Materials and methods:** Our research included 50 children (56% female and 44% male) with NS. NS was defined as the presence of edema, massive proteinuria, hypoalbuminemia and hyperlipidemia. Patients with NS were treated according to international protocol. SRNS was diagnosed in patients with idiopathic NS based on lack of complete remission despite treatment with steroids. Renal biopsy was performed in 22 patients with SRNS at the Pediatric Clinic II of the University Clinical Center in Sarajevo (UCCS). Histopathologic analyzes of renal biopsy were performed at the Department of Pathology, University Clinical Center in Tuzla (UCCT). Patients with SRNS, after kidney biopsy were treated with nonsteroidal immunosuppressant's. **Results:** Eight (36.4%) of the 22 patients who had undergone renal biopsies had minimal change disease (MCNS) and seven (31.8%) had focal segmental glomerulosclerosis (FSGS). The immunosuppressive drugs used in SRNS were Cyclosporine (CsA), Cyclophosphamide (CYC), Mycophenolat mofetil (MMF) and Rituximab (RTX). Three patients (13.6%) did not respond to any treatment and had developed end - stage renal disease (ESRD). **Conclusion:** With current treatments, some children will ultimately achieve a sustained remission with one of the second line or third line of the proposed drugs. Patients with refractory NS will go to progression towards ESRD. The rapid development of molecular genetics will give a new contribution to the pathogenesis and treatment of this disease.

Keywords: steroid-resistant nephrotic syndrome, nephrotic syndrome, immunosuppressive agents.

1. INTRODUCTION

Nephrotic syndrome is one of the most frequent glomerular diseases among children. The average incidence of NS is 2-16.9 per 100,000 children worldwide (1). NS prognosis correlates with the response to steroid therapy. There have been described three categories of the disease: steroid-sensitive nephrotic syndrome (SSNS), steroid-dependent nephrotic syndrome (SDNS), and steroid-resistant nephrotic syndrome (SRNS). The majority of children with idiopathic NS respond to steroid therapy (2). In patients with SRNS, other treatments like calcineurin inhibitors (CNIs) and Cyclophosphamide (CYC) have been used to reduce proteinuria, but their toxicities have limited their use. Mycophenolat mofetil (MMF), Rituximab (RTX) and plasmapheresis has been used in children with SRNS but the results have not been consistent in all studies (3, 4). The present study aimed to determine the demographic characteristics, renal biopsy findings, response to treatment, and prognosis in pediatric patients with SRNS.

2. MATERIALS AND METHODS

The clinical records of NS-diagnosed patients were analyzed in this retrospective and descriptive study. Patients were treated at the UCCS in period from 2009 until 2016. The study was made up of all nephrotic children who were age 1-18 years, with normal kidney function, without macroscopic hematuria, symptoms of systemic disease, and with negative antinuclear antibody assay, negative viral screens and no family history of kidney disease. The exclusion criteria were included: patients under 1 year old, patients with chronic renal disease, with secondary SRNS, Hepatitis B or C, syphilis or HIV positive and positive family history of NS.

NS was defined as the presence of edema, proteinuria higher than 40 mg/ m²//hour, serum albumin less than 2.5 gr/dl, and hypercholesterolemia (5). Patients with NS were treated according to international protocol the International Study

Sex Tip Cross Tabulation

			Type		TOTAL
			SRNS	SSNS	
Sex	Male	Count	13	17	28
		% within Type	59,1%	60,7%	56,0%
	Female	Count	9	11	22
		% within Type	40,9%	39,3%	44,0%
Total		Count	22	28	50
		% within Type	100,0%	100,0%	100,0%

Group Statistics

	Type	N	Mean	Standard Deviation (SD)	Standard Error Mean
Age at the onset	SRNS	22	7,545	4,5011	,9596
	SSNS	28	4,571	3,3102	,6256

Table 1. Comparison of patient sex and age at the onset of diagnosis in patients with SRNS and SSNS

of Kidney Disease in Children (ISKDC). All patients received the first intravenous methylprednisolone and then continued therapy with oral prednisone.

SRNS was diagnosed in patients with idiopathic NS based on lack of complete remission despite treatment with steroids (6). Complete remission was defined as 24-h protein excretion <4 mg/m²/h. Partial remission was defined when proteinuria continued between 4 mg/ m²/hour-40 mg/m²/hour or between 30-300 mg/dl by multistic. Non-response was defined as a reduction in the basal proteinuria value <50%. Relapse was defined as three consecutive days of ≥3+ proteinuria, returning to the nephrotic range after achieving remission (7).

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <80 mL/min/1.73 m² used Schwartz equation (8). ESRD was defined as the need for renal replacement treatment or an eGFR <15 mL/min/1.73 m².

Renal biopsy was performed in 22 patients at our Clinic in SRNS patients. Biopsy samples were examined by light and immunofluorescence microscopy. Patients who were SRNS after kidney biopsy were treated with nonsteroidal immunosuppressants: Cyclosporine (3-6 mg / kg / day), Cyclophosphamide (2 mg / kg / day) combined with oral prednisolone. After 6 months, patients that did not respond to CsA were switched to MMF 500-600 mg/m2/day or 18 mg/kg/d (maximum 1 g) in two divided doses at least 12 months. In one case of the MCNS and one with FSGS, we used Rituximab and for one patient with FSGS plasmapheresis was applied.

The Ethics Committee of UCCS approved the study.

Statistical analyses

The analysis were performed using Student's t test and Pearson chi-square test with Yates correction for small sample. Predictive factors for a complete clinical response were determined by multivariate logistic regression analysis. The level of statistical significance was set at p<0.05. Statistical analysis were performed using statistical package SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) while the final presentation of results in tables and charts was conducted using Microsoft Excel and Word 2010 (Richmond, USA).

3. RESULTS

Out of the 22 patients with SRNS: 13 (59.1%) were boys, and 9 (40.9%) were girls, while in the group of the SSNS there were 17 (60.7%) boys and 11 (39.3%) girls. The male-female ratio in SRNS group was 1.4:1 and in the group of the SSNS 1.5:1; the difference in the number of males and females was not significant (Chi-square = 0.574; p=0.449; p> 0.05). The mean age at the first episode of NS in-patient with SRNS was 7.5±4.5, and in the group of the SSNS it was 4, 6±3, 3 years which is statistically significant difference (t=2.693; p=0.010; p<0.05) (Table 1).

At the presentation moment, 21 (95.5%) of the all SRNS patients had edema, 12 (54.5%) had arterial hypertension and 14 (63.6%) had microhematuria. In 45.5% of SRNS patients (n = 10) was present a history of allergies and atopic constitution. A respiratory tract infection may precede the diagnosis in 7 (31.8%) of the patients.

Variable	Odds ratio	95% CI	P
Age at diagnosis	0.9512	0.7660 to 1.1812	0.6508
Sex of patient	0.7623	0.1849 to 3.1440	0.7074
Hematuria	15.5933	3.7750 to 64.4107	0.0001
Hypertension	0.7616	0.1812 to 3.2024	0.7102
Atopic constitution	0.9422	0.2217 to 4.0042	0.9357

Table 2. General characteristics of patients with NS and their response to corticosteroid therapy-logistic regression analysis Odds Ratios and 95% Confidence Intervals

By using logistic regression analysis we have proved that only the presence of hematuria shows 15,6 times higher relative risk to develop resistance to corticosteroid therapy which is statistically significance (Table 2).

Renal biopsy was performed in 22 out of 50 patients with NS. MCNS was the most frequent histology, it was reported in 36, 4% patients (n = 8), 31.8% (n = 7) was with FSGS, diffuse mesangial proliferation (DMP) was in 13.6% (n = 3), mem-

HF of the renal biopsy	N (%)	CKD n (%)
MCNS	8 (36.4 %)	0 (0 %)
FSGS	7 (31.8 %)	2 (28.6%)
DMP	3 (13.6%)	0 (0%)
MPGN	3 (13, 6 %)	1 (33.3%)
MN	1 (4.5%)	0 (0 %)
TOTAL	22 (100%)	3 (13.6%)

Table 3. Histological findings (HF) of the renal biopsy and percentage of patients who developed CKD

branoproliferative glomerulonephritis (MPGN) in 13.6% (n = 3) and 4.5% (n = 1) membranous glomerulonephritis (MN). Three of them (13.6%) had developed CKD and ESRD (Table 3).

Considering both clinical and histopathologic findings of renal biopsy, we have found that out of 50 patients with NS, 72% had MCNS, where 8 cases were confirmed by kidney biopsy, and the other (28 patients) were indirectly assumed that they had MCNS due to typical clinical image of NS and a positive response to corticosteroid therapy.

Table 4. shows initial immunosuppressive therapy in patients with SRNS. The majority of patients had received CsA -13 (59.1%), but without statistical significance.

	MCNS	FSGS	DMP	MPGN	MN	TOTAL
CsA	5	6	1		1	13 (59.1%)
CYC	3	1	2	3		9 (40.9%)
TOTAL	8	7	3	3	1	22 (100.0%)

Table 4. Initial immunosuppressive therapy in patients with SRNS

4. DISCUSSION

The percentage of patients with SRNS in our study (34%) was significantly higher than that of 10-20% of SRNS patients reported in the KDIGO study (9). Our Clinic is a tertiary health institution that receives complicated patients with NS from all over the Federation of Bosnia and Herzegovina, except the Tuzla Canton.

In our study, in SRNS group the ratio between male and female was 1.4:1 and in the SSNS group was 1.5:1 (Table 1). Many studies reported that NS was more common in males than in females (12, 13). Statistical significant difference in the mean age of the NS first episode between boys and girls was observed compared with SSNS and SRNS. Similar results are from New Zealand, Netherlands and Iran studies (12, 13, 14). The mean age of SRNS at presentation (7.5 years) in our children was comparable to other studies (15, 16).

The number of SRNS patients increased with the increase of age. In our research, the highest percentage of patients (31.8%) was in the age group over 10 years. However, by using logistic regression analysis we have realized that only the presence of microhematuria shows statistically significant influence on the appearance for steroid resistance (Table 2). Numerous studies show that male gender, age greater than 8 years and the presence of hematuria is statistically significantly more frequent in the SRNS group than in the SSNS group (17, 18).

The three most frequently seen histological findings on the renal biopsy in our study were MCNS, FSGS and MPGN (Table 3), as it is in other studies (19). Unlike other studies that examine this issue, in our study 22.2 % of patients with MCNS did not respond to an initial treatment of steroids, while in literature only 2% of patients with MCNS do not respond to steroids. An explanation for the MCNS low sensitivity to corticosteroid therapy in our study could lie in the ambivalence of the histological finding. Namely, due to the unavailability of the electronic microscope, it was not possible to confirm that it was actually MCNS. It was also noted that at least 20 glomeruli are needed in a biopsy to confidently exclude lesions that are affecting only 5% of them; hence, there is a possibility of missing an FSGS lesion or another (20). In our study, the histological FSGS characteristic was present in 31.8% of SRNS, which is also consistent with date from literature (21). In our study, three patients had MPGN. MPGN is observed in 7% of children and 12% of adults with idiopathic NS in USA (21). Most of these patients have type I disease. However, the incidence of MPGN type I is decreasing progressively in developed countries, which could be explained by the change in environmental factors, especially a decline of infections (22). We had only one child with MN. In generally, MN is rare in children (<5%) (22, 23).

The treatment of SRNS is extremely difficult. SRNS patients in our research achieved a complete remission with Cyclosporine in 45.45% of cases. The literature states that the success of achieving remission with CsA can be expected in 30 to 75% of patients with SRNS (18, 24, 25). In our study, SRNS patients with MCNS achieved high remission by CsA use. For FSGS patients in our study, Cyclosporine was also the most effective: complete remission was achieved in 42.8% of patients. The only patient in our study with MN received CsA and achieved complete remission. Other studies have shown that CsA can induce partial or complete remission in 50–60% of patients (26). In 40.9 % of patients with SRNS in our study, we have applied CYC in the absence of other therapeutic options (MMF or RTX). Three patients with MCNS were receiving CYC as well; two had achieved complete remission, while one had no response. Out of the three patients with MPGN who were receiving CYC, two had achieved partial remission, and one had no response. For the patient with MPGN without the response to CYC we have applied immunosuppressive therapy, but there was no effect and the child had developed ESRD. Treatment strategies for idiopathic MPGN are controversial. Two patients with DMP that received therapy with CYC have achieved the complete remission (Table 4). In the literature, the success rate of CYC therapy varies from 17% (27) to 43.1% (28). The KDIGO study does not recommend use of CYC in the NS therapy for children. The attitude is based on several studies that have shown no evidence of the benefits of combined CYC and prednisone therapy compared to the corticosteroids therapy alone (29).

When there were no effect of CsA and CYC as a secondary line of immunosuppressive drugs in therapy, MMF was used in five patients where three patients (60%) achieved partial remission. MMF has been used in children with SRNS and SDNS (30) but the results have not been consistent in the study. KDIGO guidelines recommend using CINs as first-line therapy for children with SRNS due to none know nephrotoxic side effects of MMF (31).

Although steroids and CNIs are the cornerstone treatments, the literature suggests that RTX looks as efficient and safe alternative in childhood (32). We applied RTX to one MCNS patient who was resistant to all other immunosuppressive medications and the child introduced the remission that lasted for 3 years. Despite the successful and safe use of RTX in the treatment of patients with SRNS which report different studies (4, 32), in our study, there was no systematic use of this biological therapy in SRNS patients. The reasons for this are the inability to procure the same drug in our country for nephrology patients.

In our study 12 relapses occurred in five (35.7%) of 14 SRNS patients that had achieved complete remission; all of

these relapses occurred after termination of CsA treatment. In other studies relapse rate ranges from 40% to 70% (33, 34) within the first year after achieving remission, which is similar to our results.

There were not many patients with serious complications of nephrotic syndrome or with undesirable effects of therapy in our study. The serious unwanted effects of nephrotic syndrome therapy that we have noted was cerebrovascular insult in a 9-year-old patient with FSGS on CsA therapy, in fact that was "Reversible posterior leukoencephalopathy syndrome" and is described by other authors such as Zang and colleagues (35). The boy recovered without any consequences.

Three patients (13.6%) who did not react to any therapy developed ESRD after 7.3 years on average. In the FSGS cases (28.6% of FSGS patients), both patients entered ESRD after 8 years of therapy, while in one patient with MPGN (33.3% of MPGN patients) ESRD occurred after 6 years. Our patients with nephrotic syndrome and FSGS who failed to achieve remission with any treatment progress to ESKD in 50%. The same are the results in the literature (18, 36).

For the patient with ESRD, the ultimate treatment goal is renal transplantation. Currently kidney transplant results are excellent: one-year survival of the transplant is 93%, 10-year in 80%, and average graft survival is about 15 years (37). In our study, two patients with FSGS have undergone renal transplantation. Additional efforts are needed to develop the donor network and transplantation medicine in our country and enable children with SRNS the needed kidney transplantation.

5. CONCLUSION

The optimal treatment of SRNS remains controversial. SRNS can be managed well with various immunosuppressant drugs such as CYC, CsA, MMF, and RTX and steroids. Rituximab is a relatively new drug in the treatment of SRNS in children and certainly takes time to demonstrate its efficiency and long-term potential side effects. In our study, remission was achievable with CsA in many cases. In addition, we suggest that MMF could be useful for treating SRNS with fewer side effects. Treatment should be individualized according to the clinical presentation, underlying histopathology and social conditions of the children. The rapid development of molecular genetics will give a new contribution to the pathogenesis of this disease and for predicting responsiveness to immunosuppressive treatment. Multicenter clinical trials are needed to improve current treatments and prevent acute and long-term complications.

• **Declaration of Interest:** All authors declare no conflicts of interest.

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