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CLINICAL PROFILE OF PEDIATRIC PATIENTS WITH STEROID-RESISTANT NEPHROTIC SYNDROME TREATED BY CYCLOPHOSPHAMIDE, CYCLOSPORIN A, MYCOPHENOLATE MOFETILE AND TACROLIMUS IN HASAN SADIKIN GENERAL HOSPITAL

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ABSTRACT

Background: Steroid-resistant nephrotic syndrome is a major cause of chronic kidney disease in children and adolescents. These diseases require appropriate management, while in some developing countries; the availability of agents recommended by international guidelines is very limited. **Research objectives:** To determine and describe the patient profiles of pediatric Steroid Resistant Nephrotic Syndrome (SRNS) that use Cyclophosphamide (CPA), Cyclosporine (CyA), Tacrolimus, and Mycophenolat Mofetil (MMF) in Dr. Hasan Sadikin Hospital (RSHS), Bandung as a tertiary hospital in West Java, Indonesia. **Methods and materials:** This research used a retrospective study with cross-sectional study design, total sampling method and medical record of pediatric (1-18 years old) patients from January 1st 2017–September 31st 2019 who were diagnosed as SRNS. **Results :** From 99 subjects that belonged to inclusion criteria, 35.4% pediatric SRNS patients were in the age group 6-10 years and 60.6% were males. Laboratory profiles showed among all population, ureum <100 mg/dL were found as high as 97%, creatinine 0.3-1.0 mg/dL (71.7%), albumin >2.5 gr/dL (51.5%), negative hematuria (68.7%), protein dipstick < 3 (50.5%), and LFG > 90 mL/min/1.73 m² (79.8%). The patients generally had use CPA (87.9%) and remission <6 month (51.5%). **Conclusion:** Profiles of pediatric patients are important to diagnose and prognose SRNS. By using these approaches, it is feasible to access and detect the most effective treatment for SRNS.

Keywords: *Steroid-resistant nephrotic syndrome, laboratory profile, remission, cyclophosphamide, cyclosporine, mycophenolate mofetil, tacrolimus, pediatric.*

INTRODUCTION

Nephrotic syndrome (NS) is the most common glomerular disease in children.¹ Nephrotic syndrome has an incidence of 7-10 cases per 100,000 children and a prevalence of 16 cases per 100,000 children.² About 80% of NS sufferers are steroid-sensitive nephrotic syndrome (SSNS), 20% are SRNS.³ Patients who have been diagnosed with SRNS, even though the percentage is smaller than SSNS, will get a heavier burden. Patients with SRNS have a worse prognosis and suffer from more severe complications, both from their own illness and the side effects of their treatment.⁴ About a half of SRNS patients will develop terminal renal failure within 1-4 years⁵, and excessive treatment can lead to infertility.⁶

To reduce the burden and complications of NS, especially SRNS, it is important to know which drugs are effective in achieving short remission times. Data from Kidney Disease Improving Global Outcome (KDIGO) shows SRNS treatment with a combination of Cyclophosphamide (CPA) and low-

dose prednisone produces remission as much as 56% and suppress recurrence by 72%.^{7,8} KDIGO also suggested a combination of Cyclosporine (CyA), low-dose prednisone and Angiotensin-Converting Enzyme Inhibitor (ACE-I) with a quite good remission rate of 69%.^{7,9} High-dose prednisone and mycophenolate mofetil (MMF) can be given if there is still no remission.¹⁰ Complete remission rate of 23-62%, a partial remission rate of 23-62% has been demonstrated by MMF treatment.^{7,11}

The effectiveness of SRNS treatment varies from patient to patient, so in addition to the time of remission; it is necessary to know the clinical profile of patients who tend to experience remission using certain drugs. Data from research at Cipto Mangunkusumo Hospital (RSCM), the Department of Child Health Sciences (IKA) in 2003-2010 states that the clinical profile of SRNS patients who tend to remission with CPA treatment are patients with a range of 1-6 years of age, have a type of secondary SRNS, Intravenous (IV) treatment route, and those with no history of hematuria.¹²



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Currently, the study report on the clinical profiles of pediatric SRNS patients, particularly in Dr. Hasan Sadikin Bandung who received various types of therapy for SRNS is still limited. Then, the data entry of SRNS patient entries in the last 3 years (2017-2019) is more complete than in previous years, so the results of research on SRNS patient profiles are expected to be better. In addition, the burden and complications that will be experienced by patients, of course, require knowledge from clinicians in order to determine the prognosis of this disease appropriately and plan administration of the procedure correctly and quickly.

METHODS

The study was conducted using a quantitative descriptive design study (cross-sectional). The object of the research is secondary data taken retrospectively from all (total sampling) medical records of SRNS patients in Kenanga Clinic, RSUP Dr. Hasan Sadikin Bandung. All research was conducted after obtaining an Ethics Letter issued by the Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran. The data collection process took place in September-October 2019.

The inclusion criteria of this study was all medical records of pediatric patients who are registered as new patients from 1 January 2017 to 31 September 2019, and diagnosed SRNS recorded in the SRNS register of the Department of Children RSHS. Then excluded if the data is incomplete (at least there are data identity, age, gender, laboratory profiles, type of therapy use, and remission time) or unreadable.

The variables used in this study were patient characteristics (age, gender, body weight, height), laboratory profiles (ureum, creatinine, albumin, proteinuria, hematuria, and LFG), type of therapy, and remission time, which is obtained by examination of uPCR <200 mg/g (<20 mg/mmol) or <1+ protein in the urine dipstick in 3 consecutive days in the first 4 weeks of treatment, the analysis was done descriptively by calculating the amount and percentage.

RESULT

The number of samples obtained in this study was 99 patients. The most SRNS diagnosed

subjects in this study came from the age group of 6-10 years (35.4%), were male (60.6%), the average height was 115.27 cm, and the average body weight was 26.73 kg. This could be seen in Table 1.

Table 1 Characteristic of Pediatric with SRNS

Characteristic	N	%
Sex		
Male	60	60.6
Female	39	39.4
Age Group		
1-5 Years	30	30.3
6-10 Years	35	35.4
11-18 Years	34	34.3
Height (average,range)	115.27	(52-167)
Weight (average,range)	26.73	(6-70)

The description of laboratory examination of SRNS patients in RSHS could be seen in Table 2. Most of the subjects had urea levels <100 mg/dL (97%). Then the highest creatinine and albumin levels were in the categories 0.3-1.0 mg/dL, (71.7%) and > 2.5 gr/dL (51.5%) respectively. Patient subjects without hematuria were the most, 68.7% followed by dipstick protein <3 (50.5%), and GFR> 90 mL/min / 1.73 m² (79.8%).

Table 2. Laboratory Profiles of Pediatric with SRNS

Laboratory Profiles	n	%
Ureum (mg/dL)		
<100	96	97
≥100	3	3
Average(SD)	29.79(24.83)	
Creatinin (mg/dL)		
<0.3	20	20.2
0.3-1.0	71	71.7
>1.0	8	8.1
Average(SD)	0.71(1.02)	
Albumin (g/dL)		
<2.5	48	48.5
≥2.5	51	51.5
Average(SD)	2.27(1.23)	
Hematuria		
Yes	31	31.3
No	68	68.7
Protein Dipstick		
≥3	49	49.5
<3	50	50.5
GFR (mL/min/1.73 m²)		
<15	5	5.1
15-30	1	1.0
31-60	3	3.0
61-90	11	11.1
>90	79	79.8
Average(SD)	159.67(132.37)	



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Table 3 shows the number of remission patients and the type of therapy (immunosuppressants) used in the treatment of SRNS. The data showed that most subjects had remission less than 6 months (51.5%), had remission (64.6%) and used cyclophosphamide (CPA) immunosuppressants (87.9%).

Table 3. Remission time and type of therapy

Type of Therapy	Remission Time			Total
	<6 Month	≥6 Month	Resistant	
Mycophenolate mofetile (MMF)	2	0	0	2(2.0%)
Cyclophosphamide (CPA)	48	13	26	87(87.9%)
Cyclosporine (CyA)	0	0	7	7(7.1%)
Tacrolimus	1	0	2	3(3.0%)
Total	51(51.5%)	13(13.1%)	35(35.4%)	99(100%)

DISCUSSION

From this study, most subjects diagnosed with SRNS in RSHS from January 2017-September 2019 came from the age group of 6-10 years (35.4%), male sex (60.6%), average height 115.27 cm, and an average body weight of 26.73 kg. This finding is similar to Hidayati *et al.* who found that 70.7% of SRNS patients were male, but different in the age group. The age group was most in the 2-6 years age group (48.8%).¹² But in the study of Subandiyah *et al.* found that 68.7% of SRNS patients age group was >6 years.¹³ The average height in this study is at 115.27 (24.45) cm with a range of 52-167. This is almost similar to the study of Dewi Kumara Wati *et al* found that the average height of the child in the NS case was 120 (18.25), with a range of 88-150.¹⁴

The ureum level of this study was mostly found in the category <100 mg/dL (97%) with average (SD) is 29.79 (24.83). This finding was similar enough with Hidayati *et al* that found average (SD) of ureum is 28.4 (21.5).¹²

The highest creatinine levels in this study were 0.3-1.0 mg / dL, (71.7%), and had an average (SD) of 0.71 (1.02). For creatinine, Hidayati *et al* listed average and SD of 0.7 (0.7).¹² Whereas in the study of Narayan *et al*, the average creatinine was 0.92(0.25).¹⁵ In children, the ratio of urine protein and creatinine or the ratio of albumin and creatinine to urine when it becomes very useful for diagnose and to rate the function of kidney because it is difficult to collect urine for 24 hours.¹⁶

Albumin levels in this study had the most subjects at levels > 2.5 gr/dL (51.5%), and had an average (SD) of 2.27 (1.23). This was found to be different in the study of Subandiyah *et al*, who found that 87.5% SRNS patients had albumin levels <2 gr / dL.¹³ Whereas in the Hidayati *et al* study, it was found to be different, albumin levels had an average (SD) of 1.9 (0.8).¹³ In the Narayan Prasad *et al* study, albumin levels had an average (SD) that was higher than this study, which was 2.7 (1.1).¹⁵

In this study, the number of subjects without hematuria was greater than that in hematuria (68.7%). This was found to be the same as the study of Subandiyah *et al*, where there was no hematuria (73.3%).¹³

Glomerular capillary walls consist of three structural elements which constitute a barrier to permeability: endothelial cells are separated by fenestrae, glomerular basement membranes consist of a network of protein matrices, and special epithelial cells (podocytes) are connected to each other through interdigitating slit networks of the diaphragm. Usually, albumin size proteins (69 kd) and larger are excluded from filtering, the limitation is highly dependent on the integrity of the diaphragm gap.¹

In nephrotic syndrome, the glomeruli appear to change greatly. Adjacent podocytes appear to coalesce together, assuming morphology is flattened to resemble feet, resulting in a soluble factor that triggers capillary changes resulting in albuminuria, protein leakage and even hematuria and affect the function of creatinine and ureum clearance.¹⁷ But in this study, it is found that the most of the subject has a normal function of kidney, it is because most of the type of idiopathic NS is minimal change disease (MCD), although when there is significant intravascular volume depletion, the function of kidney would be diminished.¹⁷

In this study, the highest number of subjects had dipstick protein <3 (50.5%). This was found to be different in the study of Subandiyah *et al* who found that the subjects of SRNS dipstick ≥3 protein patients were 73.3%.¹³ NPHS2 gene mutation, as the main mutation that occurs in patients with SRNS, causes part of the glomerular capillary wall to malfunction or loss of diaphragmatic slit. The loss of components in the diaphragm slit causes leakage of



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protein through the slit pore podocytes so that proteinuria occurs.¹⁸

Most subjects in this study had LFG levels > 90 mL / min / 1.73 m² (79.8%) and average (SD) of 159.67 (132.37). This was found to be the same in the study of Subandiyah *et al.*, where LFG levels > 80 mL / min / 1.73 m² were 73.3%.¹³ For average (SD) in Hidayati *et al.* Studies found in the range 110.1 (50.3).¹² Research results can differ according to different regional demographic factors.¹⁷ This variable is needed in examinations to assess kidney function caused by SRNS or by the effects of treatment, to see the patient's tendency in subsequent prognosis, whether it will lead to ESRD or experience improvement.^{6,19}

In this study, it was found that most subjects experienced remission for less than 6 months (51.5%), experienced remission both <6 months and ≥6 months (61.6%) and used immunosuppressant CPA (87.9%). This was found to be the same in the research of Hasan Okutesh *et al.* that the subject who experienced the most remissions was 75.3% and used CPA immunosuppressants (72.6%).²⁰ In the Hidayati *et al.* study, treatment using CPA IV, subjects experienced a remission of 71.4%.¹² This is almost similar to our study which achieved a remission of 70.1% CPA. But in a randomized control trial study conducted by KDIGO, the use of a combination of CPA with prednisone yielded a rate of 56%.^{7,21} The results of the effectiveness of different remissions due to different research demographics as well. Then in the RSHS the use of CPA is still widely used because the price is cheap and the remission level is still quite high²², although in KDIGO, the use of CPA is not recommended, because the research is still less effective than CyA and has side effects such as infertility.²³

As for CyA, MMF, and Tacrolimus, the remissions produced are 100%, 0%, and 33%. This is different when compared to research at ISKDC, where for CyA, MMF and Tacrolimus, remissions range from 69%, 23-62%, and 86%.⁷ Different things were also shown in the research of Hasan Okutesh *et al.* in which remissions for MMF and CyA ranged from 29% and 48.3%.²⁰ The percentages in the two studies were found to be different due to different demographic factors and the number of patients.

Tacrolimus was compared with CyA in one study and did not show significant differences in proteinuria control. The frequency of nephrotoxicity, hypertension, and diabetes mellitus did not differ between the two CyA and Tacrolimus in this trial. Hypertrichosis and gingival hyperplasia are more common with cyclosporine compared with tacrolimus.⁷

This study also has limitations. One of them is difficulty in reading and accessing patient medical records. In addition, researchers cannot retrieve data for more than 2017-2019 because the time limit for data collection and medical records before 2017 is incomplete.

This research can be further developed with a longer period of time and a larger sample or other variables that have not been studied. Future studies can also make relationships/tabulations between variables that have been found.

CONCLUSION

The effectiveness of SRNS treatment varies from patient to patient, so in addition to the time of remission, it is necessary to know the profile of patients who tend to experience remission using certain drugs. It is hoped that this research can provide an overview of the profile of patients who tend to remission using certain drugs.

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