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Original Article

Risk factors for relapse in pediatric nephrotic syndrome

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Abstract

Background Nephrotic syndrome (NS) is the most common kidney disease in children and is characterized by edema, massive proteinuria, hypoalbuminemia, and hyperlipidemia. High relapse rate remains a major problem in the management of this syndrome.

Objective To identify risk factors for relapse in pediatric nephrotic syndrome.

Methods This study was carried out in the Wahidin Sudirohusodo Teaching Hospital in Makassar, South Sulawesi, Indonesia, from January to August 2017 using complete medical records of children diagnosed with NS. Subjects were divided into 2 groups: 1) relapsed NS or 2) non-relapsed NS. The following potential risk factors for relapse were analyzed using Chi-square test: age, sex, nutritional status, hypertension, serum creatinine level, and infection at the time of established diagnosis of NS.

Results A total of 142 children with NS who fulfilled the inclusion criteria aged 1.4 to 17.5 years were included in the study. Subjects were mostly boys (66.2%), with a male: female ratio of 1.95:1. The relapsed NS group had 80 cases (56.3%) and the non-relapsed NS group had 62 cases (43.7%). Statistical analysis revealed that nutritional status was a significant risk factor for relapse in pediatric nephrotic syndrome ($P<0.05$).

Conclusion Nutritional status is an independent risk factor for relapse in pediatric nephrotic syndrome. **[Paediatr Indones. 2018;58:238-42; doi: http://dx.doi.org/10.14238/pi58.5.2018.238-41**].

Keywords: *nephrotic syndrome; children; relapse risk factors*

Nephrotic syndrome (NS) is characterized by massive proteinuria (>40 mg/m^2/h), heavy hypoalbuminemia (<2.5 g/dL), edema, and usually accompanied by hypercholesterolemia >200 mg/dL, based on the *International Study of Kidney Disease in Children* (ISKDC) criteria.[1] Nephrotic syndrome is the most common kidney disease of children generally occurring in school-aged children less than 14 years of age.[1] Reports from the USA and UK showed that NS affects 2-7/100,000 children per year, with a prevalence of 12-16/100,000 children; whereas a report from Indonesia showed that NS affects 6/100,000 children under 4 years of age per year. The ratio of boys to girls was reported to be 2:1.[2-4]

The majority of children (90%) with idiopathic NS (INS) usually have minimal change NS (MCNS) on histopathologic findings, and 95% or more respond well to therapy with steroids.[5] However, INS is a chronic kidney disease generally tending to

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relapse. Remission is defined as absent (-) or trace (±) proteinuria (or proteinuria < 4 mg/m^2/hour) for three consecutive days in a week. Relapse was defined as urine protein ≥ 2+ (or proteinuria >40 mg/m^2/hour) for three consecutive days in a week in patients previously in remission.[3]

The International Study of Kidney Disease in children (ISKDC) originally reported a previous relapse rate of 60%,[1] but a later report showed a relapse rate increase of up to 76-90%, with a frequent relapse rate up to 50%.[3] There are several risk factors for relapse based on previous studies including age, sex, nutritional status, hypertension, creatinine levels, and infection at the time of diagnosis of NS. Therefore, if such risk factors in children with NS could be identified on admission to the hospital, better strategies for the management of pediatric nephrotic syndrome could be implemented in the future. This study was conducted to determine which variables were risk factors for the occurrence of relapse in pediatric nephrotic syndrome in Indonesia.

Methods

This study was conducted in the Department of Child Health, Wahidin Sudirohusodo Teaching Hospital, Makassar, South Sulawesi, Indonesia, from January to August 2017. We studied 142 children with INS hospitalized during the study period.

All patients who fulfilled the ISKDC criteria for the diagnosis of NS including massive proteinuria (or proteinuria >40 mg/m^2/hour or 50mg/kg/day; urinary protein/creatinine ratio of >2.0; or dipstick ≥ 2+), hypoalbuminemia (serum albumin < 2.5 g/dL), edema, and hypercholesterolemia (serum cholesterol >200 mg/dL) were further analyzed. Relapse was defined as urine protein ≥ 2+ (or proteinuria >40 mg/m^2/hour) for 3 consecutive days in a week in patients who had been in remission previously during the first 6 months of steroid therapy. Non-relapse was defined as absent (-) or trace (±) proteinuria (or proteinuria < 4 mg/m^2/hour) for 3 consecutive days in a week within 6 months of steroid therapy.

Nutritional status is the state of nutrition which is defined based on body weight parameter toward the body height based on *CDC-NCHS 2000* standard for children aged > 5 years and based on WHO for children aged ≤5 years. Hypertension is defined as systolic and/or diastolic blood pressure was above 95 percentage based on age and gender, for 3 consecutive times. Normal creatinine was define as the level of creatinine of 0.3 -1.2 mg/dL and increased creatinine if the level of creatinine is > 1.2 mg/dL. Infection is a disease that the patients had on admission beside the relapsed NS diagnosed, which was written on medical record, including pneumonia, diare, dermatological infection, and urinary tract infection. Drop out are those who did not come to the next control.

The subjects were divided into two groups: group I was comprised of children with INS who had relapsed after receiving up to 6 months of steroid therapy, whereas group II was comprised of children with INS who had sustained a state of remission for at least the first 6 months after receiving steroid therapy.

Patients with systemic and chronic diseases, congenital nephrotic syndrome, steroid resistance, and incomplete medical records (demographic and laboratory data) were excluded from the study. The following variables were recorded for all subjects: age, sex, height, body weight, history of infection, blood pressure, and laboratory findings such as serum protein, serum albumin, serum cholesterol, serum creatinine, complete blood count, as well as urinalysis, at the time of the NS diagnosis.

Data were presented by using univariate analysis on a categorical scale expressed as frequency with a corresponding percentage and the differences between groups was compared by using Chi-square test (bivariate analysis), using *SPSS* software. Variables that yielded a P value of < 0.05 by bivariate analysis were considered to be significant and subsequently further analyzed by multivariate analysis. The study was approved by the Research Ethics Committee of Wahidin Sudirohusodo Teaching Hospital, Makassar Indonesia.

Results

A total of 142 children with INS were included in this study. The majority of patients (66.2%) were 5 years of age or more, ranging from 1.4 to 17.5 years, with a mean age of 8.5 years. There were 94 (66.2%) boys and

48 (33.8%) girls, with a male: female ratio of 1.95:1. Eighty (56.3%) subjects belonged to the relapsed group and 62 patients (43.7%) to non-relapsed group. We noted that 56.3% of cases had normal nutritional status, 73.2% had normal blood pressure, and 63.4% had no evidence of infection at the time of diagnosis. Laboratory results showed that the majority of patients (90.1%) had normal creatinine levels and half of them (50.7%) had hematuria. The characteristics of subjects are shown in **Table 1**.

The possible risk factors for relapse were compared between the two groups. Chi-square test revealed no statistically significant difference in sex or age between the two groups. Also, no statistically significant differences between the relapsed and non-relapsed groups were seen in hypertension, infection, serum creatinine level, or hematuria. However, a statistically significant difference in subjects' nutritional status was observed between the relapsed and non-relapsed groups (P=0.02). Significantly greater percentages of undernourished and poorly nourished patients were in the relapsed group compared to the non-relapsed group (**Table 2**).

Table 1. Characteristics of subjects

Characteristics	(N=142)
Sex	
Male: female ratio, n (%)	94: 48 (66.2 : 33.8)
Age at diagnosis, n (%)	
≥ 5 years	94 (66.2)
< 5 years	48 (33.8)
Nutritional status, n (%)	
Normal	80 (56.3)
Undernourished	52 (36.6)
Poorly nourished	10 (7.0)
Hypertension, n (%)	
Yes	38 (26.8)
No	104 (73.2)
Creatinine level, n (%)	
Normal	128 (90.1)
Increased	14 (9.9)
Hematuria, n (%)	
Yes	72 (50.7)
No	70 (49.3)
Infection at diagnosis, n (%)	
Yes	52 (36.6)
No	90 (63.4)
Diagnosis, n (%)	
Relapsed	80 (56.3)
Non-relapsed	62 (43.7)

Table 2. Comparison of possible risk factors for relapse between the relapsed and non-relapsed groups

Variables	Group		P value
	Relapse (n = 80)	Non-relapse (n = 62)	
Sex, n (%)			
Male	56	48	0.277
Female	24	24	
Age at diagnosis, n (%)			
≥ 5 years	57	46	0.697
< 5 yearS	23	16	
Nutritional status, n (%)			
Normal	37	43	0.023
Undernourished	36	16	
Poorly nourished	7	3	
Hypertension, n (%)			
Yes	22	16	0.821
No	58	46	
Creatinine level, n (%)			
Normal	73	55	0.615
Increased	7	7	
Hematuria, n (%)			
Yes	41	31	0.883
No	39	49	
Infection, n (%)			
Yes	31	21	0.549
No	31	41	

Discussion

The frequency of relapse in idiopathic NS was 56.3% in our study, with a boy to girl ratio of 1.95:1. This ratio was similar to that of Constantinescu et al. who reported 1.8:1.6 But our frequency of relapse was lower than that of Mishra et al.7 in India and Subandiyah6 in Indonesia, who reported 59.3% and 65.9%, respectively.

In our study, the age of patients at the time of diagnosis was classified into either the ≤ 5 years of age group or >5 years of age group. A bivariate analysis revealed no statistically significant difference between the relapsed and non-relapsed groups in age at the time of diagnosis (P<0.697), similar to a study by Ali et al. (P=0.708).9 While the mechanism of INS remains unclear, it was hypothesized that INS may be caused by impaired T-cell function and the presence of abnormal T-cell clones producing chemical mediators as circulating glomerulotoxic lymphokines. These mediators increase permeability of the glomerular basement membrane, resulting in proteinuria. Abnormal T-cells are suspected to be cloned in the thymus, which is most active in childhood.[10]

We noted that the only statistically significant difference between the relapsed and non-relapsed groups was for nutritional status (P=0.023), with a higher percentage of poorly nourished subjects experiencing relapse. In contrast, Noer et al. found no statistically significant difference according to nutritional status of their patients. We found no statistically significant differences between the relapsed and non-relapsed groups in serum creatinine or hematuria levels, with P=0.615 and P=0.883, respectively. However, Sarker et al. found low levels of protein and serum albumin to be risk factors for frequent relapse.[3]

The limitations of our study were due to: 1) the patient data being taken retrospectively from medical records, 2) the recorded data being only six months after diagnosis, and 3) the non-relapsed group not further monitored after six months of steroid therapy. However, the strength of our study was that we excluded from further analysis those with incomplete medical record data as well as those who dropped out.

In conclusion, nutritional status of patients at the time of diagnosis may be used as risk factor for relapse in pediatric nephrotic syndrome. Clinicians should provide nutritional therapy if the NS patient is poorly nourished and reevaluate at least six months after steroid therapy. We suggest that further studies be performed without a six-month time limit to further assess other possible risk factors for relapse in pediatric nephrotic syndrome.

Conflict of Interest

None declared.

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