ORIGINAL ARTICLE **Open Access**

Profile of Minimal and Non-Minimal Change Nephrotic Syndrome in Children: A Cross-Sectional Study

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ABSTRACT

Introduction: Idiopathic nephrotic syndrome (INS) is the most common kidney disease in children. Histopathological features classify the disease into minimal change nephrotic syndrome (MCNS) and non-minimal change nephrotic syndrome (NMCNS). Clinical and laboratory characteristics are considered to be useful in estimating the underlying pathological changes. This study aimed to assess the spectrum of clinical and laboratory profiles in children suffering from MCNS and NMCNS.

Methods: This was a cross-sectional study using medical records of patients hospitalized at Dr. Wahidin Sudirohusodo Central General Hospital and Hasanuddin University Teaching Hospital from January 2016 to August 2018. Subjects were classified into MCNS and NMCNS groups and evaluated for age, sex, hypertension, degree of edema, degree of hematuria, proteinuria level, cholesterol level, albumin level, urea level, and creatinine level. Data were analyzed by using chi-square, fisher's exact test Mann Whitney analysis, multivariate by logistic multiple regression analysis, and diagnostic test.

Results: Of the 36 subjects enrolled, 10 (27.8%) had MCNS, and 26 (72.2%) had NMCNS. Bivariate analysis showed significant differences in hypertension (p=0.020; OR=12.3; 95% CI 1.35-111.61) and hematuria (p=0.018; OR=7.7 ; 95% CI 1.52-39.75).

(Continued on next page)

Article history:
Received: 27 June 2020
Accepted: 14 August 2020
Published: 30 August 2020

GREEN MEDICAL JOURNAL
E-ISSN 2686-6668

Published by :
Faculty of Medicine
Universitas Muslim Indonesia

Address:
Jl. Urip Sumoharjo Km. 5, Makassar
South Sulawesi, Indonesia

Mobile number:
+62822 9333 0002

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Multivariate analysis indicated that only hematuria is a significant predictor (p=0.014; OR=7.778; 95% CI 1.522 – 39.754). The diagnostic test of NMCNS showed hematuria sensitivity at 77% and specificity at 70% with a positive predictive value of 87% and a negative predictive value of 46%.

Conclusion: Our study showed that hematuria is a sensitive predictor of NMCNS.

Keywords: Hematuria; nephrotic syndrome; child; diagnostic tests

Introduction

Idiopathic nephrotic syndrome (NS) is the most common kidney disease in children. NS is a group of clinical symptoms consisting of massive proteinuria (>40 mg/m2 BSA/hour or 50 mg/kg/day or protein/creatinine ratio in random urine >2 mg/mg or dipstick >2+), hypoalbuminemia <2.5 g/dL, edema, and could be accompanied by hyperlipidemia > 200 mg/dL.[1,2]

NS without the existence of systemic disease is called primary NS, which is found in 90% pediatric cases. The incidence of NS is up to 2 to 7 cases per year in 100,000 children aged below 16 years old with a cumulative prevalence of 16 in 100,000 children. According to a study by Yoseph, it is more commonly found among boys (74.4%) than girls (25.6%) with a ratio of 2.9:1.[3] Minimal change disease is the most common (46.4%) but has the best prognosis. Primary NS could not be deemed as a benign disease because data showed that up to 60% of patients experience frequent relapses and need long-term immunosuppressive therapy.[4]

International Study of Kidney Disease in Children (ISKDC) made clinical and laboratory characteristic guidelines to estimate the lesion type in children with NS. Those clinical and laboratory characteristics are age at first episode, sex, hypertension, hematuria, mean creatinine, C3 complement, and serum cholesterol level. Histopathological features represent a response to steroid therapy. Most MCNS are steroid-sensitive, while NMCNS are mostly steroid resistant.[5]

A study that assesses the comparison between clinical and laboratory aspects of MCNS and NMCNS has never been conducted in Indonesia, so it is hoped that this study will further our knowledge for better clinical application in the future. Therefore, this study is necessary to be done and used in tailoring a more comprehensive treatment. This study aimed to assess the spectrum of clinical and laboratory profiles in children suffering from MCNS and NMCNS.

Methods

Study design, location and time

This study was a cross-sectional study in patients who were recently diagnosed with NS and old NS patients who had never undergone biopsy.

The study was conducted in Dr. Wahidin Sudirohusodo Central General Hospital and Hasanuddin University Teaching Hospital from January 2016 to August 2018, after receiving approval from the Clinical Research Ethics Committee.

Population and subjects

Subjects were chosen using a purposive sampling technique from all pediatric patients with MCNS and NMCNS. Inclusion criteria were patients with MCNS, NMCNS, or idiopathic NS aged 1-18 years old. Exclusion criteria were patients with secondary NS or coexisting systemic disease, congenital malformation affecting renal function, and incomplete data in the medical records.

Data recording

Renal biopsy was done on patients who were recently diagnosed with NS and old NS patients who had never undergone biopsy according to their medical records. Based on histopathology results, patients were divided into the MCNS and NMCNS group. Next, assessment of age, sex, blood pressure, degree of edema, degree of hematuria, proteinuria level, serum cholesterol level, serum albumin level, serum urea level, and serum creatinine level was done in both groups.

Data analysis

Univariate analysis was used to describe the characteristics of the basic data of the study. Unpaired T-test was used for numeric data with normal distribution, while the Mann Whitney test was used for data with abnormal distribution or ordinal data. X^2 test (*Chi-Square*) or Fisher Exact test was used to compare two categorical variables between two or more independent groups. The significant p-value was considered as less than 0.05. Afterward, double logistic regression analysis was performed to estimate the probability of each clinical symptom and determine the probability of MCNS or NMCNS based on clinical symptoms. A diagnostic test was performed to explain the calculation of sensitivity, specificity, positive predictive value, and negative predictive value.

Results

From 36 subjects, 10 children (27.8%) had MCNS and 26 children (72.2%) had NMCNS, consisting of 21 children (58.2%) with focal segmental glomerulosclerosis, 2 children (5.5%) with total segmental glomerulosclerosis, and 3 children (8.5%) with global diffuse glomerulosclerosis in table 1.

The number of boys in MCNS and NMCNS groups was 7 (70%) and 15 (57.7%) with no statistically significant difference (p=0.706). The Median age of the MCNS group was 13 (8-17) years old and NMCNS group 13 (6–17) years old, without a statistically significant difference (p = 0.736) (Table 2).

Hypertension was found on 1 child (10%) in the MCNS group and 15 children (57.7%) in the NMCNS group. There was a significant difference in the number of children with hypertension between two groups with p = 0.020 (p< 0.05) and odds ratio (OR) 12.3 in table 2.

Table 1. Study subjects' characteristics

No	Subjects' Characteristic	Total (N: 36)
1	Sex (%)	
	Boys	22 (61%)
	Girls	14 (39%)
2	Age (year)	
	Mean ± SD	12.5 ± 3,00
	Median	13
	Minimum-maximum	6 – 17
3	Hypertension (%)	
	Yes	16 (44%)
	No	20 (56%)
4	Proteinuria (%)	
	Massive	33 (91.7%)
	No	3 (8.3%)
5	Albumin level (gr/dL)	
	Mean ± SD	2.0 ± 0.77
	Median	2.1
	Minimum - maximum	1.0 – 3.0
6	Degree of edema (%)	
	Mild	11 (30.5%)
	Moderate	22 (61%)
	Severe	3 (8.5%)
7	Cholesterol level (mg/dL)	
	Mean ± SD	414.3 ± 161.88
	Median	394.5
	Minimum - maximum	132 – 832
8	Hematuria (%)	
	Yes	23 (63.8%)
	No	13 (36.2%)
9	Creatinine level (mg/dL)	
	Mean ± SD	0.80 ± 0.63
	Median	0.64
	Minimum - maximum	0.16 – 3.55
10	Ureum level (mg/dL)	
	Mean ± SD	44.5 ± 25.56
	Median	41,5
	Minimum - maximum	12 – 118
11	Histopathology (%)	
	Minimal Changes	10 (27.8%)
	Focal Segmental Glomerulosclerosis	21 (58.2%)
	Total Segmental Glomerulosclerosis	2 (5.5%)
	Global Diffuse Glomerulosclerosis	3 (8.5%)

Massive proteinuria was found on 9 children (90%) in the MCNS group and 24 children (92%) in the NMCNS group, although the difference was not statistically significant (p = 1.000) (Table 2).

The median albumin level was 2.5 (1.1 – 3) gr/dL for the MCNS group and 1.95 (1.0 – 3.0) gr/dL for the NMCNS group, with no significant difference (p = 0.467). In the MCNS group, 4 children (40%) had mild edema, 5 children (50%) had moderate edema, and 1 child (10%) had severe edema. In the NMCNS group, 7 children (27%) had mild edema, 17 children (65%) had moderate edema, and 2 children (8%) had severe edema. There was no significant difference in the frequency of edema severity (p=1.000) (Table 2).

Table 2. The distribution between MCNS and NMCNS groups

No	Subjects	MCNS (N:10)	NMCNS (N: 26)	P-Value
1	Sex (%)			0,706
	Boys	7 (70%)	15 (57,7%)	
	Girls	3 (30%)	11 (42,3%)	
2	Age (year)			0,736
	Mean ± SD	12.94 ± 2,84	12,46 ± 3,11	
	Median	13	13	
	Minimum-maximum	8-17	6-17	
3	Hypertension (%)			0,020
	Yes	1 (10%)	15 (57,7%)	
	No	9 (90%)	11 (42,3%)	
4	Proteinuria (%)			1,000
	Massive	9 (90%)	24 (92%)	
	No	1 (10%)	2 (8%)	
5	Albumin level (gr/dL)			0,467
	Mean ± SD	2,23 ± 0,73	2,04 ± 0,78	
	Median	2,50	1,95	
	Minimum - maximum	1,1-3,0	1,0-3,0	
6	Degree of edema (%)			0,694
	Mild	4 (40%)	7(27%)	
	Moderate	5 (50%)	17(65%)	
	Severe	1 (10%)	2(8%)	
7	Cholesterol level (mg/dL)			0,560
	Mean ± SD	375,30 ± 136,33	429,38 ± 170,73	
	Median	400,50	394,50	
	Minimum - maximum	158 - 551	132 - 832	
8	Hematuria (%)			0,018
	Yes	3 (30%)	20 (76,9%)	
	No	7 (70%)	6 (23,1%)	
9	Creatinine level (mg/dL)			0,491
	Mean ± SD	0,70 ± 0,38	0,85 ± 0,70	
	Median	0,57	0,71	
	Minimum - maximum	0,40 – 1,70	0,16 – 3,55	
10	Ureum level (mg/dL)			0,138
	Mean ± SD	33,40 ± 15,11	48,80 ± 27,63	
	Median	29,50	45,00	
	Minimum - maximum	15 - 61	12 – 118	

Cholesterol level of children with MCNS and NMCNS respectively had median of 400.50 (158-551) mg/dL and 394.50 (132-832) mg/dL in table 2, which were not statistically significant (p = 0.560). The number of children with hematuria in the MCNS group was 3 (30%). But, In the NMCNS group, 20 children (76.9%) had hematuria. The difference was statistically significant (p = 0.018; OR = 7.7) (Table 2).

The creatinine level in the MCNS group had a median of 0.57 (0.40-1.70) mg/dL. Meanwhile, the median of creatinine level in the NMCNS group was 0.71 (0.16-3.55) mg/dL. However, the difference was not significant (p = 0.491). The median of the urea level in the MCNS group was 29.5 (15-61) mg/dL. In NMCNS group, the median urea level was 45 (12-118) mg/dL, producing no statistically significant difference (p = 0.138) (Table 2).

Double logistic regression analysis showed that only one variable was truly significant, which was hematuria with p = 0.014 and OR 7.778 (95% CI 1.522-39.754). This was an adjusted odds ratio, which means that children with NS who experience hematuria have a 7.778 times higher risk of NMCNS (Table 3).

Table 3. Double logistic regression analysis results in MCNS and NMCNS groups

No	Variable	B	S.E.	df	Sig.	Exp (B)	95%CI for EXP (B)
1.	Hematuria	2.051	0.832	1	0.014	7.778	1.522 - 39.754
2.	Constant	-0.154	0.556	1	0.782	0.857	

B: regression coefficient, S.E: standard error, Exp (B): Adjusted Odds Ratio

The sensitivity results showed that NS patients with symptoms of hematuria were NMCNS of 77%, while the results of specificity showed that NS patients who were not hematuria were MCNS of 70%. The results of positive predictive values indicate that NS patients with symptoms of hematuria are NMCNS of 87%, while the negative predictive value of SN patients who are not accompanied by hematuria is not as NMCNS of 46% in table 4.

Table 4. Diagnostic test of hematuria symptoms in MCNS and NMCNS groups.

Hematuria	Group		Total
	MCNS	NMCNS	
Yes	3 (30%)	20 (76.9%)	23 (63.8%)
No	7 (70%)	6 (23.1%)	13 (36.2%)
Total	10 (100%)	26 (100%)	36 (100%)
Sensitivity : 77%,	Specitivity :70%,	PPV : 87%,	NPV :46%

Discussion

ISKDC reported that 84.5% of idiopathic NS in children is MCNS. This is different from the result of our study, where 10 children (27.8%) had MCNS and 26 children (72.2%) had NMCNS.

Our result is in accordance with a study done by S.Indupriya in India where MCNS was found on 37.9% subject and NMCNS on 62.%.[6] A similar result was obtained by a study by Yoseph A in Semarang, where MCNS was found on 16.7% subject and NMCNS on 83.3%.[3] Another study done by Lucknow in India showed that FSGS was the most common type (38%), followed by MCNS (30%). This study in comparison with other studies from other countries and centers showed variable histological patterns, although at the moment it seems that minimal change disease is the most common variation of NS in children. These differences may be related to racial, genetic, and environmental characteristics.[7]

Based on the result, there were 22 boys (61%) among subjects and only 14 girls (39%). This is in accordance with several studies. In a study by Nilawati in RSUP Sanglah Denpasar, 73.5% of the subjects were boys and 26.5% were girls with a ratio of 2.7:1. [8] In a study by Swarnali et al. in Srilanka, 58% of the subjects were boys and 42% were girls.[9] In NS, cellular immunity dysfunction is thought to happen in the thymus, and this abnormality is more commonly found among boys. [10] Based on bivariate analysis, there is no significant difference in the distribution of subjects sex. This is in accordance with a previous study by Yoseph A, where p= 0.432.[3]

Analysis of the mean age showed no significant difference between MCSN and NMCSN groups. The previous study by Yoseph A obtained similar results, with p=0.492.[3] In that study, the mean age of subjects in MCNS group was 12.94 ± 2,84 years old and in NMCNS group 12.46 ± 3.11 years old. In a study by Swarnali et al., the mean age of subjects with MCNS was 4.2 years old while the mean age of subjects with NMCNS was 5.08 years old, with most subjects being under 8 years old.[9] NS is found 15 times more often in children than in adults. A hypothesis states that NS is caused by the formation of abnormal T cell clone producing mediator that increases the permeability of the basal membrane. This abnormal T cell clone exists in the thymus and is more active in children compared to adults.[11–13]

Analysis of hypertension frequency showed a significant difference between MCNS and NMCNS groups. However, the difference was not significant in logistic regression. A study done by Yoseph A stated that there is a significant difference in hypertension frequency between MCNS and NMCNS groups with p = 0.040,[3] while in the study Swarnali et al., no significant difference was found in the frequency of hypertension.[9] The mechanism of hypertension in NS is associated with the damage of nephrons of the collecting tubule, causing water and salt retention. Primary renal sodium retention causes plasma and extracellular fluid volume expansion. Stimulation of renin-angiotensin and activation of aldosterone and antidiuretic hormone will cause hypertension.[14]

Analysis of proteinuria degree showed no significant difference between the two groups. A study by Yoseph A showed a similar result (p=0.976).[3] Proteinuria is caused by a change in glomerular capillary and is commonly related to the lesion type.

According to ISKDC, a decrease in serum albumin level is a mandatory laboratory criterion to establish the diagnosis of NS. All subjects showed a decrease in serum albumin level, ranging from 1.1-3.0 g/dL in MCNS group and from 1.0-3.0 gr/dL in NMCNS group (p = 0.467).

This is in accordance with a study by Yoseph A and Swarnali et al., which also obtained insignificant results.[3,9] Hypoalbuminemia in NS is due to the protein loss from glomerular filtration, even protein with small molecule.[11–13] Analysis of the degree of edema showed no significant difference between MCNS and NMCNS groups with $p > 0.05$, in accordance with the result of the study by Yoseph A.[3] Compared to adolescents and adults, neonates and younger children have a greater proportion of total body and interstitial (IS) fluid volume, which can double or triple because of edema related to NS.[15] Based on the underfilled theory, massive proteinuria causes hypoalbuminemia, which then decreases the oncotic pressure. A study by Novina, et al., showed a negative correlation between serum albumin level and percentage of edema.[16]

In this study, the cholesterol level in MCNS group was slightly higher than in NMCNS group. This is in accordance with the study by Swarnali et al. where the mean cholesterol level in MCNS group was 450.64 mg/dL and in NMCNS group 504.03 mg/dL.[9] Milne reported that the total cholesterol level in NS patients might increase up to 1000mg/dL. In this study, the highest cholesterol level in MCNS group was 551 mg/dL and in NMCNS group 832 mg/dL ($p > 0.05$). This is in accordance with previous studies by Yoseph A and Swarnali et al. which showed an insignificant result.[3,9] A decrease in plasma albumin levels will stimulate hepatic lipoprotein synthesis. A decrease in blood lipid clearance as a result of the loss of lipase enzyme as a lipid catalyst due to damaged tubules also explains hypercholesterolemia in NS patients.

Analysis of hematuria frequency showed a significant difference between MCNS and NMCNS groups with $p = 0.018$ and OR 7.7. Based on logistic regression analysis with several other variables, hematuria was the only significant variable with $p = 0.014$ and OR 7.778. In a study by Swarnali et al., hematuria was found on 50% subjects in MCNS group and 52,6% subjects in NMCNS group, and the difference was not statistically significant.[9] In NMCNS, the damage of the Glomerular Filtration Barrier (GFB) is more severe, causing larger protein molecules to pass along with albumin, including red blood cells.

Analysis of the mean creatinine level showed no significant difference between MCNS and NMCNS groups with $p = 0.491$. This is in accordance with the previous study by Swarnali et al. which found no significant difference of mean creatinine level between MCNS and NMCNS groups with $p = 0.100$.[9] A Study by Jeremy Kiffel, et al. showed that FSGS is one of the important causes of increased creatinine levels in children and adults.[17] Besides, according to ISKDC, 25% of FSGS patients develop end-stage renal failure in 5 years. Increased creatinine is caused by ongoing immunologic process, hemodynamic hyperfiltration in maintaining glomerulus, protein and phosphate diet, persistent proteinuria, and systemic hypertension. Analysis of mean urea level showed no significant difference between MCNS and NMCNS groups, in accordance with the study by Swarnali et al., where no significant difference was found between MCNS and NMCNS groups with $p = 0.200$.[9]

From several clinical and laboratory aspects assessed in this study, hypertension and hematuria were found to be statistically significant ($p<0.05$). However, based on logistic regression analysis, only hematuria was significant with $p= 0.014$, while other assessed factors were not statistically significant.

This could be caused by different genetic polymorphism from other studies' subjects, causing several variables to be statistically insignificant. Idiopathic NS is 3-4 times more prevalent in children with human leukocyte antigen (HLA)-DR7. In several genetic studies, the NPHS1 gene is found in MCNS. While in NMCNS (FSGS), CD2AP, ACTN4, and TRPC6 genes are found.[18]

The strength of this study is the use of 10 variables so that the obtained clinical and laboratory aspects cover almost all symptoms in NS. Besides, this study also offers data based on histopathological results. The results of this study could contribute to the recognition of clinical and laboratory aspects of MCNS and NMCNS as a consideration in treating NS in children, and reduce complications due to long-term steroid therapy.

The limitation of this study was not assessing genetic polymorphism, which could be one of the causes of MCNS or NMCNS in children.

Conclusion

The frequency of MCNS was 27.8% and NMCNS 72.2%. Our study showed that hematuria is a sensitive predictor of NMCNS. These data could serve as a consideration for clinicians to recommend a continuous follow up when encountering children with NS and clinical symptoms of hypertension and hematuria to avoid complications of long-term steroid therapy.

Conflict of Interest

No potential conflict of interest relevant to this article was reported. We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgment

We are thankful to Prof. dr. Husain Albar, Sp.A(K) and dr. Jusli Aras, M.Kes, Sp.A for their support and encouragement for the study. We are also thankful to dr. A. Dwi Bahagia, Ph.D., Sp.A(K), Head of The Department Pediatric Faculty of Medicine Hasanuddin University for his constant encouragement.

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