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Risk Factors of Relapse in Nephrotic Syndrome

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Abstract **Original Research Article**

Background: Nephrotic syndrome (NS) is a kidney disease with high incidence, typically in young children. NS is a disease of relapse, and it is a major problem to manage the cases with relapse. So, it is very important to find out such children who are prone to develop relapse. Hence, this study was carried out to find out the risk factors of relapse in children with NS. ***Objective:*** To determine the risk factors of relapse in patients with nephrotic syndrome. ***Methods:*** This case-control study was conducted at the Department of Paediatric Nephrology and Department of Paediatrics, Dhaka Medical College Hospital, for 12- months following ethical approval. A total of 100 NS children (age: 2-12 years) were enrolled in this study, among them 50 were cases (NS with relapse) and 50 were controls (initial attack of NS with no relapse within one year of disease onset). After obtaining written informed consent from parents/legal guardian, a detailed history, thorough clinical examination and necessary investigations were carried out in each patient during initial episode of NS. Data analysis was done by SPSS 26.0. ***Results:*** Mean age of the cases and controls was6.11±3.01years and 6.96±3.14years, respectively (p=0.169), with an overall boys-girl ration of 1.3:1. Maximum cases (56.0%) had infrequent relapse. Lower age of onset was prevalent among case group than control (31.96±15.15 months vs 46.48±27.76 months; p=0.002). Infection was significantly more prevalent among cases than controls (68.0% vs 38.0%; OR=3.46; p=0.003), UTI (38.0% vs 10.0%; OR; 5.52; p=0.001). Cases had significantly higher history of atopy (52.0% vs 30.0%; OR=2.53; p=0.025). Higher serum cholesterol (441.62±61.46 mg/dL vs 389.12±72.18 mg/dL; <0.001) and lower serum albumin (15.74±2.20 gm/L vs 17.30±2.99 gm/L; p=0.004) were seen in cases than control. ***Conclusion:*** Lower age of onset, history of atopy, infection, higher serum cholesterol and lower serum albumin level during initial attack were associated with relapse in NS children. However, further larger study is recommended.

Keywords: Nephrotic syndrome, higher serum cholesterol, focal segmental glomerulosclerosis, lower serum albumin.

INTRODUCTION

Nephrotic syndrome (NS) is the most common renal disease in children. It is defined by nephrotic-range proteinuria (≥40 mg/m^2/hour or urine protein/creatinine ratio ≥200 mg/mL or 3+ protein on urine dipstick), hypoalbuminaemia (<25 g/L) and oedema. NS is the most common childhood kidney disease worldwide, with a reported incidence of 2–7/100,000 children [1]. The incidence of NS is higher in children of Asian descent compared with those of European descent, whereas African American and Hispanic children are more likely to be resistant to treatment and have worse outcomes [2]. In the India subcontinent it is estimated at 9-10 per 100000 population, but this figure will vary according to the ethnic mix of the population [3]. NS is the most common glomerular disease, followed by AGN and Henoch-Schonlein purpura (HSP) in Bangladesh [4].

Frequent relapses of nephrotic syndrome are defined as children having two or more relapses within six months of disease onset after the initial episodes of four relapses in a twelve months period. Infection is an important cause of relapse in minimal change nephrotic syndrome. Evaluation, prevention and treatment of infection, which could reduce proteinuria without use of steroid[5]. History of atopy, low serum albumin and total protein level at the time of initial attack were significantly associated with frequent relapse [6]. 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 [7]. Relapsed NS patient experienced a long period treatment and became dependent on steroids, which might cause side effects such as short stature, overweight, osteoporosis, and cardiovascular

disease, Cushing syndrome, psychologic disorder and decreased immune system [8].

NS is a common renal disease seen in children. Most children with steroid sensitive NS have multiple relapses and a significant percentage also develop steroid dependent NS. So, it is very important to find out such children who are prone to develop frequent relapse. Bangladesh has very limited study regarding this issue. So, this study is very important to predict the risk factors of relapse in the patients of nephrotic syndrome.

Objective

General Objective:

To determine the risk factors of relapse in patients with nephrotic syndrome.

Specific objectives:

- To determine the socio-demographic characteristics of each group
- To evaluate the risk factors e.g. age of onset, history of atopy, infection, serum cholesterol and serum albumin during initial episode among relapse patients.

METHODOLOGY

Study Design: Case-control study.

Study Place: Department of Paediatric Nephrology and Department of Paediatrics, Dhaka Medical College Hospital.

Study Period: July 2021-June 2022

Study population: Children from 2-12 years of age with nephrotic syndrome admitted to aforementioned department were grouped as

- Case: Patients of nephrotic syndrome with relapse
- Control: Patients with initial attack of nephrotic syndrome with no relapse within one year of disease onset

Sample Method: Purposive sampling

Sample Size: The sample size will be determined by following formula:

$$n = \frac{\{Z_\alpha\sqrt{2P_2(100-P_2)}+Z_\beta\sqrt{P_1(100-P_1)+P_2(100-P_2)}\}^2}{(P_1-P_2)^2}$$

Where,
n = Calculated sample size

Z_α = Z-value of standard normal distribution at 95% confidence level = 1.96

Z_β = Z-value (one tail) of standard normal distribution at a definite power = 0.84 at power 80%

$$\text{So, } n = \frac{\{1.96\sqrt{2*21(100-21)}+0.85\sqrt{31(100-31)+21(100-21)}\}^2}{(31-21)^2}$$

P_1 =Infection was present among relapse patient was 31% (Albar *et al.*, 2018) P_2 = Infection was present among non-relapse patient was 21%

Therefore, the required sample size =273.17~274

Due to time, resource constrain and pandemic Covid-19 situation 100 samples were taken for this study, 50 children of nephrotic syndrome with relapse were enrolled as cases and 50 children with initial attack nephrotic syndrome with no relapse within one year of disease onset were enrolled as controls.

Selection Criteria:

Inclusion criteria of cases:

- Age: 2 to 12 years
- Patient with relapse both frequently and infrequently
- Willing to participate

Inclusion criteria of Controls:

Age: 2 to 12 years

- Patient with initial attack of nephrotic syndrome with no relapse within 1 year of disease onset
- Willing to participate

Exclusion criteria:

- Steroid resistant nephrotic syndrome (SRNS)

Secondary nephrotic syndrome like systemic lupus erythematosus (SLE), Henoch Schonlein purpura (HSP), Alport syndrome, IgA nephropathy, etc.

Data Collection Tools:

- Data was collected through predesigned questionnaire
- Tools for physical examination
- Informed written consent form in Bangla
- Informed written consent form in English

Data Collection Procedure:

This study was conducted at Department of Paediatric Nephrology and Department of Paediatrics in Dhaka Medical College Hospital. All subjects underwent a complete history taking and physical examination during initial episode of nephrotic syndrome 50% of similar age and sex fulfilling selection criteria were taken as cases and 50% fulfilling criteria were taken as controls. A questionnaire (Appendix C) was prepared considering key variables like demographic data, clinical presentation, clinical findings and investigations. After selection of the patients, aims, objectives and procedure

of the study was explained with understandable languages to the patients' parents. Risks and benefits were also made clear to parents. Then they were encouraged to participate voluntarily and were allowed to withdraw themselves from the study. Then informed written consent (Appendix A) was taken from each parent of the patients.

Data processing and analysis:

After collection of data, they were edited thoroughly along with checking and re- checking. Data were processed, compiled and analysis was done with Statistical Package for Social Sciences (SPSS) version 26.0 for windows 10. Statistical significance was set as 95% confidence level. Socio-demographic characteristics, clinical and laboratory parameters were reported. Continuous data were expressed as mean and standard deviation and categorical data were expressed as frequency and percentage and comparisons were assessed by student t-test and chi-square test for continuous and categorical variables respectively. Odds ratio and multivariate logistic regression analysis were done to see the association of risk factors with relapse. A probability (p) value of <0.05 were considered statistically significant.

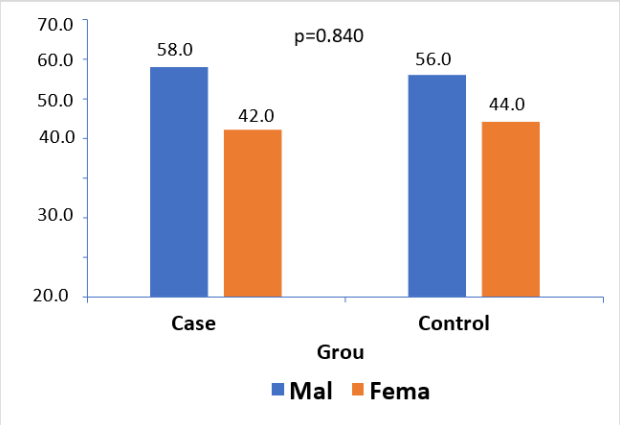
RESULT

Mean age of the cases were 6.11±3.01 years while among control were 6.96±3.14 years (*p*=0.169).

Table-1: Distribution of study population groups according to age (n=100)

	Case (n=50)	Control (n=50)	*P* value
Mean Age (±SD), years	6.11±3.01	6.96±3.14	0.169

P value measured by independent sample t-test



***P* value measured by chi square test**

Figure 1: Distribution of study population according to gender (n=100)

Among cases about 58% were boys and 42% girls. Among controls, 56.0% were boys and rest 44.0% girls. In total, boys were slightly more than girls with boys-girls ration of 1.3:1.

Age of onset of nephrotic syndrome among controls were significantly more (46.48±27.76 months) than cases (31.96±15.15 months). History of atopy significantly higher in case group (p=0.025, OR=2.53), infection is significantly associated with case group (p=0.003; OR=3.46), presence of UTI significantly higher in case group compared to control (38% vs 10%, p=0.001, OR=5.52). No significant difference was found in terms of hypertension and hematuria of the patients between groups.

Table-2: Outcome variables among case and controls (n=100)

Variables	Case (n=50)	Control (n=50)	OR	*P* value
Age of onset, months (Mean±SD)	31.96±15.15	46.48±27.76		0.002†
History of atopy	26 (52.0%)	15 (30.0%)	2.53	0.025*
Infection:	34(68.0%)	19(38.0%)	3.46	0.003*
Presence of UTI	19(38.0%)	5(10.0%)	5.52	0.001*
Upper resp. tract infection	15(30.0%)	14(28.0%)		0.826*
Hypertension	14 (28.0%)	11 (22.0%)		0.488*
Hematuria	8 (16.0%)	5 (10.0%)		0.372*

†*P* value measured by independent sample's t-test

**P* value measured by chi square test

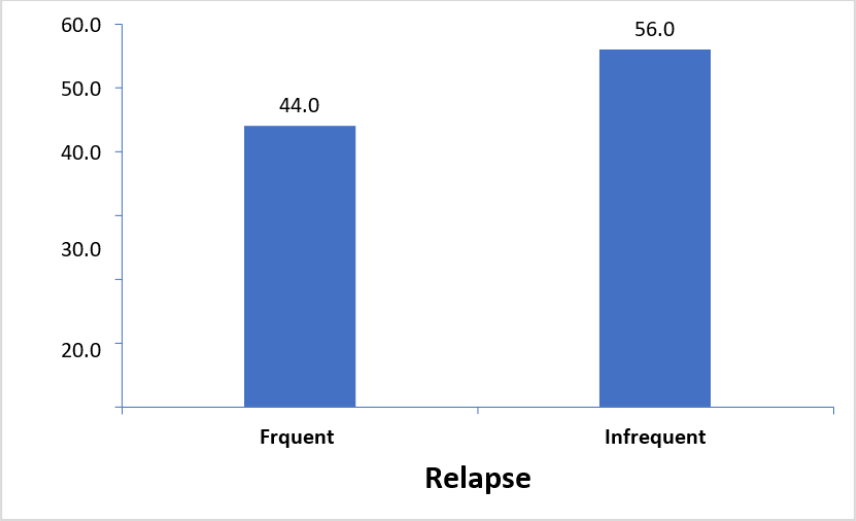


Figure-2: Frequency of frequent and infrequent relapse among cases (n=50)

Among 50 cases, 22 patients (44.0%) had frequent relapse and rest 28 patients (56.0%) had infrequent relapse.

Age of onset significantly lower in frequent relapse cases compared to control group (p=0.043). History of atopy, infection were significantly higher in frequent relapse group compared to control (p<0.05), in rest of the factors there was no significant difference between frequent and control (p>0.05).

Table-3: Outcome variables between frequent relapse patients control group (n=72)

Variables	Frequent relapse (n=22)	Control (n=50)	*P* value
Age of onset, months (Mean±SD)	33.3±17.2	46.5±27.7	0.043†
History of atopy	15 (68.2%)	15(30.0%)	0.002*
Infection: Presence of UTI	15(68.2%) 8(36.4%)	19(38.0%) 5(10.0%)	0.018* 0.002*
Upper resp. tract infection	7(31.8%)	14(28.0%)	0.743*
Hypertension	9 (40.9%)	11(22.0%)	0.099*
Hematuria	5 (22.7%)	5(10.0%)	0.150*

**P* value measured by chi square test
†*P* value measured by Unpaired t-test

Age of onset significantly lower in infrequent relapse cases compared to control group (p=0.008). Infection were significantly higher infrequent relapse compared to control (p<0.05), in rest of the factors there was no significant difference between infrequent relapse patients and control group (p>0.05).

Table-4: Outcome variables between infrequent relapse cases and control group (n=78)

Variables	Infrequent relapse (n=28)	Control (n=50)	*P* value
Age of onset, months (Mean±SD)	30.9±15.5	46.5±27.7	0.008†
History of atopy	11 (39.3%)	15(30.0%)	0.404*
Infection: Presence of UTI	19(67.8%) 11(39.3%)	19(38.0%) 5(10.0%)	0.011* 0.015*
Upper resp. tract infection	8(28.6%)	14(28.0%)	0.957*
Hypertension	5 (17.9%)	11(22.0%)	0.664*
Hematuria	3 (10.7%)	5(10.0%)	0.921*

**P* value measured by chi square test
†*P* value measured by Unpaired t-test, *significant

Table-4.8 showed that lower age of onset (<24 months) (p=0.01, OR=0.259), infection (p=0.006, OR=0.232), patients with history of atopy (p=0.008, OR=0.222) and low albumin level (<15gm/L) (p=0.025, OR=0.314) were associated with relapse in nephrotic syndrome.

Table-5: Multivariate logistic regression to predict the risk factors of relapse

Variables	S.E	p-value	OR	95%CI
Age of onset (<24 months)	.522	.010	.259	.093-.722
Infection	.531	.006	.232	.082-.656
Patient with history of atopy	.566	.008	.222	.073-.674
Low albumin (<15gm/L)	.518	.025	.314	.114-.866
High Cholesterol (>400mg/dl)	.530	.132	.450	.159-1.271

DISCUSSION

In this study 50 patients with relapse NS taken as cases and another 50 patients with initial attack nephrotic syndrome patient with no relapse within 1 year of disease onset as control. Mean age among relapse cases was slightly lower (6.11±3.01 years) than the controls (6.96±3.14 years); p=0.169. This finding is consistent with the findings of other studies.

The number of boys was found slightly higher (57.0%) than girls (43.0%). Boys were predominant in other studies [10].

Among the studied cases boys to girl's ratio was 1.33:1. Age of onset of nephrotic syndrome among controls were significantly more (46.48±27.76 months) than case (31.9±15.15 months). Infection was more prevalent among cases (68.0%) than control (38.0%) which is statistically significant (p=0.003). Sarker *et al.*, showed significantly higher prevalence of infection among frequent relapse nephrotic syndrome patients [9].

History of atopy, presence of UTI was significantly higher in case group than control. Mean serum albumin was significantly higher in control group (17.30±2.99 gm/L vs 15.74±2.20 gm/L); p=0.004. Mean serum cholesterol was significantly higher among cases than controls (441.62±61.46 mg/dL vs 389.12±72.18 mg/dL); p<0.001.

This study suggests that IRNS were more than the FRNS. This is in line with the findings of researcher [11]. Hypertension is another factor significantly associated with FR in previous but this study had no significant association [11,12].

CONCLUSION

This study was carried out to find out the risk factors of relapse in nephrotic syndrome children. In this study, maximum cases had infrequent relapse. Among controls, age of onset was significantly higher than the cases, while history of atopy, infection e.g. UTI was found significantly higher among cases. Hence, it can be concluded that lower age of onset, history of atopy, infection, high serum cholesterol and low serum albumin level during initial attack were the risk factors of relapse in nephrotic syndrome patients.

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