

Predictors of Relapse in Idiopathic Nephrotic Syndrome in Children Presenting to a Tertiary Center

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Abstract

Background and Aim: Idiopathic nephrotic syndrome (INS) is a disease of relapse and remission in children in which about 20-30% of the patients may experience a single episode in their lives while the rest suffer from relapse. Some factors contribute to relapse. The objective of this study was to explore the predictors of relapse in INS.

Methods: A prospective longitudinal study was conducted in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from September 2015 to August 2016. One hundred and ten patients with the first episode of INS were uninterruptedly enrolled in this study. After screening and subsequent confirmatory diagnosis, the patients were treated with a single morning dose of oral prednisolone 60 mg/m²/day for 6 weeks followed by oral prednisolone 40 mg/m² every alternate day for the subsequent 6 weeks. The total number of relapses within six months after the initial episode was collected in a data collection sheet. Every relapse was correlated with age of onset, sex, initial serum albumin level, fasting serum cholesterol level, and time to response in the initial attack. The association between relapse and its potential risk factors was investigated using logistic regression analysis.

Results: The study found that INS was significantly associated with sex and age ($p < 0.05$). Male children were 3.04 times (95% CI= 1.09- 8.45, $P=0.03$) more likely to experience relapse. Furthermore, children with respiratory tract infection had a higher chance of relapse (OR= 4.43, 95% CI= 1.26-15.53, $P=0.02$). Lower cholesterol levels (≤ 500 mg/dl) were found to be a protective factor (OR= 0.13, 95% CI= 0.04-0.54, $P=0.005$) in this study. The chance of relapse was higher in children who responded after 2-4 weeks of starting treatment compared to those who responded in less than one week ($p < 0.005$).

Conclusion: The study found that the first episode INS had a higher risk of relapse in boys with respiratory tract infection and in patients who needed more than two weeks of prednisolone treatment to achieve remission.

Keywords: Children; Frequently Relapsing; Predictors; Idiopathic Nephrotic Syndrome.

Conflict of interest: The authors declare no conflict of interest.

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Introduction

Nephrotic syndrome (NS) is characterized by a triad of massive proteinuria (>40 mg/m²/hour or 1gm/m²/day), hypoalbuminemia (<2.5 mg/dl), and hyperlipidemia (serum cholesterol >200 mg/dl) (1,2). NS is 15 times more common in children than in adults (3). It is a quite common clinical condition in Bangladesh usually affecting young children (4).

According to the International Study of Kidney Diseases in Children (ISKDC), oral prednisolone is the drug of choice in idiopathic nephrotic syndrome (5).

In this study, approximately 90% of the children with MCD used oral prednisolone at a dose of 60 mg/m² for 6 weeks followed by oral prednisone 40 mg/m² every alternate day for another 6 weeks. Unfortunately, the rate of relapse was high (60%–75%) with a significant percentage of patients becoming frequent relapsers (FRs) or steroid-dependent (SD). Relapse is associated with a high incidence of complications, causes anxiety in patients, and is associated with a heavy financial burden. It is difficult to predict the course of the disease after treating the first episode. Another International Study of

Kidney Disease in Children (ISKDC) analyzed the factors at presentation that correlated with future outcomes and found that the number of relapses within the first 6 months was a strong predictor of future relapses (6). This study was conducted to evaluate the factors at presentation that could predict the relapse pattern in the first year after diagnosis.

Methods

Ethical approval

This prospective longitudinal study was carried out in the Department of Pediatric Nephrology, BSMMU from September 2015 to August 2016. The protocol of the study was approved by the institutional review board of the university. Informed consent was obtained from the children's parents or legal guardians before enrollment. Moreover, the participants consented to publishing the data obtained through their participation.

Inclusion and exclusion criteria

A total of 110 patients aged 1-16 years that suffered from the first episode of INS and responded to treatment with oral prednisolone were selected through convenient sampling. The participants who presented with atypical features like rash, joint pain, hematuria, and hypertension or did not respond to the standard dose of oral prednisolone within 4 weeks were excluded from the study. NS patients with impaired renal function, hypertension and hypocomplementemia were also excluded from this study.

Patients' characteristics

The study patients were divided in two groups, viz. outpatient department (OPD) and inpatient department (IPD) groups. Initially, one hundred and ten (110) consecutive patients with INS were included in this study. Detailed history, relevant examination, and investigations were obtained from each patient in both groups. After screening and subsequent confirmatory diagnosis, all patients were treated with a single morning dose of oral prednisolone 60 mg/m²/day for 6 weeks followed by oral prednisolone 40 mg/m² every alternate day for another 6 weeks. Seven patients were lost to follow-up and six patients were excluded from this study due to lack of response to oral prednisolone 60 mg/m²/day within four weeks. Finally, 97 (N) patients that comprised of 54 (57.7%) OPD and 43 (44.3%) IPD patients were followed up under this study. Relapse was considered by using bed side urine for albumin 2+ or more for 3 consecutive days in a week.

Data collection, management and statistical analyses

Detailed history-taking and relevant examinations were done for every patient in both hospitalized and outpatient departments using a semi-structured questionnaire. The parameters of interest were collected using data collection sheets, exposed into Excel spreadsheets, and analyzed with SPSS version 20 using descriptive and

inferential statistics. P values less than 0.05 were considered significant. Continuous and categorical variables were compared using the student's unpaired t-test and chi-square test, respectively. The data were summarized using descriptive statistics for demographic characteristics and risk parameters. Mean and standard deviation (SD) were calculated for continuous variables and proportion was determined for categorical variables.

Results

More than half of the 97 enrolled patients (n=50, 52%) were from the outpatient department (OPD) of whom 36% (n=18) had no relapses, 40% (n=20) had infrequent relapses, and 24% (n=12) had frequent relapses. Less than half of the patients (n=47, 48.5%) were from the inpatient department (IPD), of whom 33.4% (n=11) had no relapses, 8.5% (n=4) had infrequent relapses, and 69.1% (n=32) had frequent relapses. As for the whole study population, 29.9% (n=29) had no relapses, 24.7% (n=24) had infrequent relapses (<2, IFRNS) and 45.4% (n=44) had frequent relapses (≥2, FRNS) during the follow-up period. There was a significant difference in outcome between the two groups (OPD and IPD) (P<0.001) (Table 1).

Table 1. Type of relapses in outpatient and inpatient department observed (N=97)

Patient sites	Number of relapse			P value
	No relapse (%)	IFRNS (%)	FRNS (%)	
OPD (n =54)	18 (33.3)	20 (44.4)	12 (22.2)	P=<0.001
IPD (n= 43)	11 (9.3)	04 (18.6)	32 (72.0)	
Total	29 (29.9)	24 (24.7)	44 (45.4)	

OPD: Out Patient Department, IPD: In Patient Department, IFRNS: Infrequent relapses of Nephrotic Syndrome, FRNS: Frequent Relapses of Nephrotic Syndrome

The patients (n=97) were categorized into three age groups: 1-2 years (n=11, 11.34%), 2-8 years (n=67, 69.07%), and > 8 years (n=19, 19.59%); moreover, 60.8% (n=59) of the patients were boys 39.1% (n=38) were girls with a male to female ratio of 1.5:1. The majority of the patients (n=67, 69%) were 2-8 years compared to 11 (11.3 %) patients aged 1-2 years and 19 (19.5%) aged > 8 years of age. Table 2 shows the patients' characteristics (demographic, clinical and biochemical) at presentation according to age group. The mean age of children with and without relapse was 5.51 ± 3.78 and 6.41 ± 3.88 years, respectively. There

Table 2. Patient characteristics (demographic, clinical and biochemical) at presentation according to age groups (N=97)

Variables	Age (years)			P value
	1-2 n (%)	2-8 n (%)	>8 n (%)	
Gender				
Male	7 (63.7)	42 (62.7)	10 (52.6)	0.716
Female	4 (36.3)	25 (37.3)	9 (47.4)	
Infection type				
UTI	4 (36.4)	9 (13.4)	1 (5.3)	0.060
RTI	7 (63.3)	20 (29.9)	6 (31.6)	0.088
Acute gastroenteritis	0 (0.0)	4 (6.0)	1 (5.3)	0.708
Peritonitis	1 (9.1)	1 (1.5)	0 (0.0)	0.202
Serum Albumin (g/l)				
≤15	6 (54.5)	40 (59.7)	8 (57.9)	0.946
>15	5 (45.5)	27 (40.3)	3 (42.1)	
Serum Cholesterol (mg/dl)				
≤500	7 (63.6)	50 (74.6)	9 (47.4)	0.075
>500	13 (36.4)	17 (25.4)	10 (52.6)	

UTI: Urinary Tract Infection, RTI: Respiratory Tract Infection

was a significant difference in the presence of relapse at onset between different age groups (Table 3).

Predictors of relapse

The predictors of relapse including sex (male and female), infection (urinary tract infection (UTI), respiratory tract infection (RTI), acute gastroenteritis, and peritonitis), serum albumin (gm/l) (≤15, >15), serum cholesterol (mg/dl) (≤500, >500) were

investigated. A significantly higher percentage of relapsers had RTI at presentation (P=0.02). Relapse had a significant association with sex (P=0.03). On the other hand, serum albumin levels (≤ 15 mg/l, >15 mg/l), serum cholesterol levels (≤500 mg/dl, >500 mg/dl), and time of relapse (<1 week, 2-4 weeks, 4-8 weeks) were significant predictors of relapse (Table 4).

Table 3. Relationship of age of onset with relapse in children with idiopathic nephrotic syndrome (N=97)

Age (years)	Relapse status		P value
	Yes (n=68)	No (n=29)	
1 – 2	11 (16.2)	0 (0.0)	0.045*
2 – 8	46 (67.7)	21 (72.4)	
>8	11 (16.2)	8 (27.6)	
Mean ± SD	5.51 ± 3.78	6.41 ± 3.88	
Total	68 (100.0)	29 (100.0)	

Chi-square test was done to measure the level of significance, SD: Standard Deviation

The risk factors were further analyzed using a logistic regression model to estimate the association between predictors and relapse. Among predictors, RTI and male sex were significant independent risk factors for subsequent relapses. Children with INS and RTI at onset were 4.4 times more likely to experience further relapses

(OR=4.4, 95% CI=1.26-15.53, P=0.02). Moreover, the chance of relapse was 3.0 times as high in boys as in girls (OR=3.04, 95% CI= 1.092-8.458, P=0.04). Low levels of serum cholesterol (≤ 500mg/dl) were a significant protective factor in this study (OR= 0.14, 95% CI= 0.035-0.541, P=0.005) (Table 5).

Table 4. Risk factors for relapses during initial attack in study subjects (N=97)

Variables	Outcome		P value
	Relapse n (%)	Non-relapse n (%)	
Sex			
Boy	46 (67.6)	13 (44.8)	0.035
Girl	22 (32.4)	16 (55.2)	
Infection type			
UTI	10 (14.7)	4 (13.8)	0.907
RTI	28 (41.2)	5 (17.2)	0.023
Acute gastroenteritis	5 (7.4)	0 (0.0)	0.134
Peritonitis	2 (2.9)	0 (0.0)	0.351
S. albumin (gm/l)			
≤ 15	54 (79.4)	17 (58.6)	0.034
> 15	14 (20.6)	12 (41.4)	
Mean (± SD)	13.38 ± 3.85	14.42 ± 3.56	
S. cholesterol (mg/dl)			
≤ 500	41 (60.3)	25 (86.2)	0.012
> 500	27 (39.7)	4 (13.8)	
Mean (± SD)	476.06 ± 144.35	423.59 ± 108.7	
Time for response (weeks)			
< 1	16 (23.5)	14 (48.3)	0.025
2 – 4	52 (76.5)	14 (48.3)	
4 -8	0 (0.0)	1 (3.4)	
Mean (± SD)	9.90 ± 5.26	8.97 ± 8.68	

UTI: Urinary Tract Infection, RTI: Respiratory Tract Infection, SD: Standard Deviation

Table 5. The result of multivariate logistic regression analysis showing the relationship between relapse and risk factors in 97 patients

Factors	OR	95% CI		P value
		LL	UL	
Age <6 years	1.93	0.606	6.168	0.265
Sex (Male)	3.04	1.092	8.458	0.033
UTI	0.37	0.074	1.820	0.220
RTI	4.43	1.264	15.539	0.020
S. Albumin (≤15 gm/l)	2.20	0.749	6.448	0.151
S Cholesterol (≤500 mg/dl)	0.14	0.035	0.541	0.005

UTI: Urinary Tract Infection, RTI: Respiratory Tract Infection, OR: odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper limit

Discussion

This prospective longitudinal study was carried out to determine the predictors of relapse in idiopathic steroid-sensitive nephrotic syndrome in children with the first episode. Ninety-seven patients with the first episode of INS were analyzed and followed for at least six months after completion of the treatment of the first episode. Subsequently, no relapse occurred in 29 patients (29.9%) within 6 months.

Twenty-four patients (24.7%) experienced < 2 relapses (IFRNS) and 44 patients (44.5%) had ≥ 2 relapses (FRNS) during the 6 months follow-up. This result was consistent with the previous findings indicating that frequently relapsing nephrotic syndrome was usual in this sub-group (7).

The mean age of the patients was 5.51 ± 3.78 years in relapse group and 6.41 ± 3.88 years in the no relapse

group. There was a significant association between age of onset and relapse rate. This finding was consistent with the results of previous studies (8,9). A recent study in India found that patients with FR were younger at the onset of the disease and the frequency of relapse decreased with age (10). Male predominance was observed in the subgroup of patients with relapse. The chance of relapse was 3.0 times higher in boys than in girls (OR= 3.04, P<0.005). Other studies also confirmed that male gender was associated with a higher risk of steroid dependency and FRNS, despite the prolongation of the steroid course, and found that male gender was a predictive factor for FR (11,12).

Previous studies reported that very low serum albumin (≤ 15 g/l) was associated with relapse (9). The present study also showed that low serum albumin (≤ 15 g/l) increased the chance of relapse by 2.2 times, which was not significant (P= 0.15) in comparison to the non-relapse group. The significance of time to response has been observed previously: the longer the time required for remission, the higher is the chance of becoming a relapser. Vivarelli et al. (2010) found patients with non-relapsing and infrequent relapsing nephrotic syndrome had a median time to remission of <7 days in contrast to >7 days in patients with frequent relapsing and steroid dependence nephrotic syndrome (13). This finding was consistent with the results of the present study and a study by Yap et al (2001) that found that an initial duration of remission of 9 days or longer was significantly associated with steroid dependency in 91 Asian children with SSNS (14). Infection was the most important risk factor for relapse. This study found that RTI (OR= 4.4, 95% CI=1.26-15.53 P=0.02) was the most common infection in the relapse group compared to other infections like UTI, acute gastroenteritis, and peritonitis, which is consistent with previous studies (15). Low levels of serum cholesterol (≤ 500 mg/dl) were a protective factor for relapse (OR =0.14, 95% CI=0.04-0.54, P=0.005). The study confirmed a constant increase in the cholesterol level, which might contribute to the progression of atherosclerosis and development to chronic renal failure (16).

Limitations

The main limitation of this study is that it was not possible to maintain a required sample size due to availability of targeted patients from multiple centers. Therefore, a convenient sampling from single center was taken that effected possible bias of this study. Further, a study with larger sample size included from multicenter is recommended to investigate all possible predictors of relapse in future.

Conclusion

This study found that the first episode of INS had a higher risk of relapse in boys with RTI, patients with higher

cholesterol levels, and children that needed more than two weeks of prednisolone treatment to achieve remission.

Conflict of Interest

The author declares no conflicts of interest.

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