Original Article

Factors Predicting Relapse in Children with First Attack Idiopathic Nephrotic Syndrome- A Hospital Based Retrospective Study

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Abstract:

Background: Nephrotic Syndrome is a disease of relapse. So, it is very important to find out such children who are prone to develop frequent relapse and the predictors responsible for relapse. This retrospective study was conducted in the department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, from September 2016 to August 2017. **Methods:** A total of 75 patients of idiopathic nephrotic syndrome (INS) with the initial attack, aged 1–18 years, were enrolled in this study. All patients were treated with prednisolone 60 mg/m2/day, single morning dose for 6 weeks, followed by 40 mg/m2 every alternate day for another 6 weeks and were analyzed and followed upfor a minimum period of six months to identify the risk factors related to relapses. **Results:** Among them, 50 (66.7%) were males, 25 (33.3%) were females, with a male: female ratio of 2:1. Ten (13.3%) children had no relapse, 18 (24.0%) had infrequent relapse, and 40 (53.3%) had frequent relapse. Children responding between 2 and 4 weeks after the start of treatment had a more chance of relapse (P = 0.002) than those who responded less than 1 week. Only urinary tract infection and respiratory tract infection are independent risk factors for subsequent relapse. Children with INS whohave UTI atonset had 1.55 times more chance for further relapse and RTI caused 1.42 times more chance for relapse. Patient with low serum albumin have 1.91 times more chance for relapse than with high albumin with in significant association. **Conclusion:** Young age at diagnosis of INS, male gender, low serum albumin and infections were predictive risk factors of multiple relapses. So, physicians should be vigilant to monitor these patients closely and counsel the families of nephrotic children regarding the prediction of subsequent relapses and ultimate outcome.

Keywords: Children; INS; risk factor.

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Introduction:

Idiopathic nephrotic syndrome (INS) is a common childhood illness characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia and oedema[1]. It constitutes about 72% to 85% of all nephrotic syndrome (NS) in children. About 90% of first episodes of INS achieve remission by corticosteroid treatment. However, 70 to 80% of these children experience relapse and 30% of them develop frequent relapse[2,3]. Multiple studies have tried to identify the risk factors associated with relapsing pattern of illness, but still remains unsolved how to predict this relapse and what should be the management strategy[4]. Different risk factors such as young age at diagnosis, male gender, initial time to response, decreased serum albumin level and haemeturia have been reported in frequent relapsing nephrotic syndrome (FRNS) and steroid dependent nephrotic syndrome (SDNS) with conflicting results. There are only few predictors of the risk of subsequent relapses after the initial response[5]. Karim et al.[6] showed that young age and low serum level of protein at onset were associated with increased frequency of relapse. Biswas et al.[7] showed that infection is an important cause of relapse in minimal

change nephrotic syndrome (MCNS), prevention and treatment of which could reduce proteinuria without the necessity of steroid treatment. Gulati et al.[8] also showed that asymptomatic UTI might be an important and undiagnosed cause of relapse. In our country illiteracy, inadequate health care facility and referral system, lack of knowledge about the disease and poor compliance cause failure of early detection and prevention of disease relapse[4]. Hence prediction and prevention of risk factors is the key to successful management of INS in children.

Methods:

This was a retrospective observational study carried out in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, from September 2016 to August 2017. A total of 75 patients of idiopathic steroid-sensitive nephrotic syndrome who fulfilled the inclusion criteria were taken. Patients with systemic and chronic diseases, congenital nephrotic syndrome, secondary causes of nephrotic syndrome, steroid resistance, hematuria, hypertension, incomplete medical records (demographic and laboratory data), hypocomplementemia and patients who had received previous immunosuppressive treatment were excluded from the study. After confirmed diagnosis and screening out of infection, all patients were treated with prednisolone 60mg/m2 /day single morning dose for 6 weeks, followed by 40 mg/m2 /day every alternate day for another 6 weeks. 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 INS diagnosis. The response to treatment was assessed by clinical examination, such as consecutive protein-free urine for 3 days, adequate diuresis, no features of edema, ascites, and infections. Response was also assessed by doing spot urinary protein creatinine ratio. Parents were counseled about disease course, treatment, prognosis, drug toxicity and trained about the interpretation and testing of urine at home by heat precipitation method. All patients were followed for at least 6 months after completion of the treatment of the first episode. Search for infection was done at every visit in both relapse and no relapsegroups. Patient characteristics (age, sex), clinical parameters (presenting complaints, treatment history, time to get remission, number of relapses within 6 months) were obtained and recorded in data collection sheet. Relapse was detected by using bedside urine for albumin 3+ or more for 3 consecutive days.

Relapse was treated by the daily dose of prednisolone 60mg/m2 /day up to protein free for 3 consecutive days. Then 40mg/m2 every alternate day for 4 weeks in infrequent relapse (IFRNS), and gradually the dose was tapered by 5mg every 2 weeks in frequent relapse (FRNS). Patients were categorized during follow-up into the following groups, depending on their response to therapy: Remission: bedside urine albumin nil for 3 consecutive days. Relapse: urine albumin 3+ or more for 3 consecutive days, having previously been in remission. IFRNS: <2 relapses within 6 months of initial response. FRNS: ≥2 relapses within 6 months of initial response or 4 or more relapses within a period of 1 year. All the investigations were done at pathology and biochemistry laboratory, BSMMU, Shahbag, Dhaka. After collection, all the data were checked and edited. Several demographic, clinical and laboratory variables were studied from hospital records and discharge paper to find out the risk factors for relapse. Data were coded, edited and enteredin a computer and were analyzed by using SPSS program. Data presented on categorical scale were expressed as frequency and corresponding percentages and were compared between groups using Chi-square ($\chi2$) test, while data presented on continuous scale were expressed as mean and standard deviation from the mean and were compared between groups by using Student's t-Test and subsequently further analyzed by multivariate regression analysis to find out risk factors for relapse where p value < 0.05 was taken as significant.

Results:

Table-I: Distribution of patients by age (n = 75)

Age in years	Number	(%)
1 - 5	46	61.3
6 – 10	24	32.0
>10	5	6.7
Mean±SD 5.3±3.3		

Out of 75 patients, majority (61.3%) were between 1- 5 years of age with a mean 5.3±3.3 years.
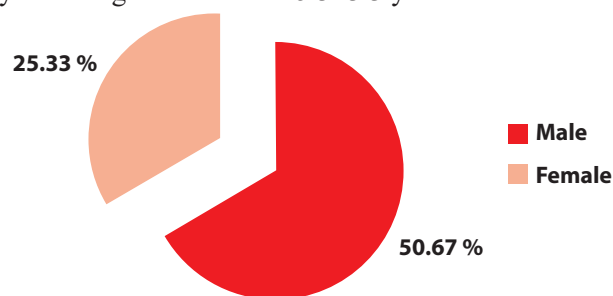
Fig-1: Pie diagram for sex distribution

Fifty of 75 subjects (66.7%) were male, and the rest (33.3%) was female giving a male-female ratio of roughly 2:1 (Fig I).

Among the study subjects atopy, family history of kidney disease, hypertension and hematuria were present in 56%, 10.7%, 20% and 16% respectively.

Table-II: Distribution of patients by socioeconomic condition (n = 75)

Socioeconomic condition	Frequency	Percentage (%)
Poor	50	66.7
Middle class	22	29.3
Upper class	03	4.0

Regarding socioeconomic condition 66.7% of the subjects came from poor socioeconomic class followed by 29.3% from middle class and only 4% from upper class.

Table-III: Distribution of patients by residence (n = 100)

Residence	Frequency	Percentage (%)
Rural	42	56
Urban	27	36
Urban slum	6	8

56% of the subjects came from rural, 35% from urban and remaining 5% from urban slum area.

Table-III: Risk factors distribution of the study patients (n = 75)

Risk factors		Number	(%)
Atopy	Present	42	56.0
	Absent	33	44.0
Family history of kidney disease	Present	8	10.7
	Absent	67	89.3
Hypertension	Present	15	20.0
	Absent	60	80.0
Hematuria	Present	12	16.0
	Absent	63	84.0

Table-IV: Patient characteristic satp resentation according to age groups (n=75)

| Parameter					
Age(years)		1-5 (n=46)	6-10(n=24)	>10(n=5)	p
Gender	Male	29(63.0)	17(70.8)	4(80.0)	0.65^{ns}
	Female	17(37.0)	7(29.2)	1(20.0)	
UTI		12(26.1)	10(41.7)	3(60.0)	0.18^{ns}
RTI		12(26.1)	8(33.3)	1(20.0)	0.75^{ns}
Peritonitis		4(8.7)	0(0.0)	0(0.0)	0.26^{ns}
SerumAlbumin(g/dl)					
Mean±SD		1.39±0.	1.35±0.	1.26±0.	0.47^{ns}
Serum Cholesterol(mg/dl)					
≤500		40(87.0)	18(75.0)	2(40.0)	$\mathbf{0.03^{s}}$
>500		6(13.0)	6(25.0)	3(60.0)	
Urinarytotalprotein (mg/dl)		3.96±1.5	5.18±1.1	5.90±3.5	$\mathbf{0.003^{s}}$

Number of days in remission
Mean±SD   13.57±5.77   7.50±2.55
0.002s ns=Notsignificant (p>0.05), s=Significant (p<0.05)
pvaluereached from Chi Squaretest for qualitative data and ANOVA test for quantitative data.

Table IV showing baseline characteristics of study subjects at presentation. The parameters such as gender, infections and serum albumin level did not differ significantly among the three age groups except serum cholesterol level and UTP   which were significantly (p=0.03) lower (≤500mg/dl) in 1-5 years age group and UTP was higher   (5.90±3.54 mg/dl, p=0.003) in children >10 years of age
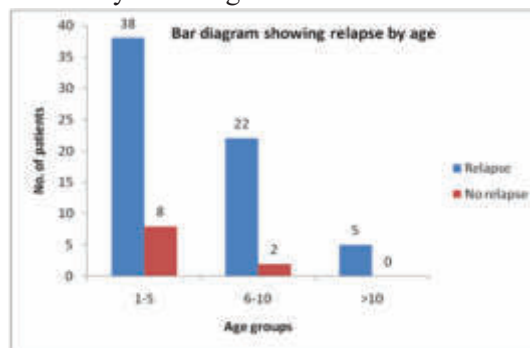
Fig-2: Bar diagram showing relapse by age

Bar diagram showing association of age of onset with relapse in study subjects. Mean age of children with relapse was 5.48 ± 3.39 and without relapse was 4.38 ± 1.90 years but there was no statistically significant difference between these two groups.

Table-V: Multivariate logistic regression analysis of risk factors for relapse.

Variables of interest	B	P value	OR	95% C.I. for OR	
				Lower	Upper
Age <6 years	0.244	0.27	1.41	0.107	4.560
Sex (Male)	0.334	0.17	1.39	0.356	5.485
UTI	**0.548**	**0.02**	**1.55**	**1.078**	**2.579**
RTI	**0.534**	**0.03**	**1.42**	**1.058**	**3.785**
Low Serum Albumin	0.648	0.64	1.91	0.124	29.243
S Cholesterol (≤500 mg/dl) 1.186		0.10	3.27	0.790	13.561

Multivariate logistic regression analysis of parameters showed only urinary tract infection and respiratory tract infection were independent risk factors for subsequent relapse. Children with INS who have UTI at onset had 1.55 times more chance for further relapse and RTI showed 1.42 times more chance for relapse. Patient with low serum albumin have 1.91 times more chance for relapse than with high albumin with insignificant association. There was also no significant relationship between serum cholesterol level and relapse.

Discussion:

The long-term outcomes of children with steroid-sensitive nephrotic syndrome are far better than a resistant disease. A sub-group of SSNS that behaves as frequently relapsing or steroid-dependent nephrotic syndrome are subjected to recurrent steroid therapy, rendering them to fatal side effects.[10] A total of 75 patients with an initial episode of INS were analyzed and followed for at least six months after the completion of treatment of the initial attack. Maximum 40 (53.3%) children had two or more than two relapse, 18 (24%) less than two relapse, 10 (13.3%) children had no relapse, 5 (6.7%) had steroid resistance and 2 (2.7%) had steroid dependence within 6 months of follow- up period. This finding is comparable with the findings of Chwat et al.[11] where frequently relapsing nephrotic syndrome being the commonest sub-group. Mean age of the patient ranges from 5.48 ± 3.39 years in relapse group and 4.38 ± 1.90 years in no relapse group. In agreement with previous studies performed by Constaninescu et al.[3] and Takeda et al.[5] no correlations were present between age at presentation and future relapses among patients with NS. On the other hand, Andersen et al.[12] and Sarker et al.4 found a significant correlation between age at presentation <4 and <5 years respectively and an increased incidence of relapses in the future. A recent study from India by Sinha et al.[13] found that patients with FR were younger at the onset of the disease, and the frequency of relapses declined with increasing age. Out of 75 patients, 50 (66.7%) were male and 25 (33.3%) were female with male-to-female ratio of 2:1. Male predominance was observed in patients with relapse. Andersen et al.[13] reported that male gender was associated with a higher risk of steroid dependency and FRNS, despite the prolongation of the steroid course. Noer et al.[13] also found that male gender is a predictive factor for FR. In this study, majority of patients (66.7%) came from poor class family, and they were significantly prone to develop FRNS than the children belong to middle and upper class. This is comparable with the finding of Biswas et al.[7] Significantly higher incidence of FRNS was found in rural children than that in urban children which was also found in a similar study done in our country.[4] Statistically significant number of children with FRNS had history of atopy. There is no comparable data but Meadow et al.[14] described those children with steroid sensitive NS had a higher incidence of atopic disorder. Takeda et al.[5] showed that low serum protein or albumin work as significant predictors for frequent relapses in future. Our study also showed that out of 75 patients, albumin level did not differ significantly among the three age groups except serum cholesterol level and UTP, which were significantly (p=0.03) lower (≤500mg/dl) in 1-5 years age group and UTP (5.90±3.54 mg/dl, p=0.003) was higher in >10 years age groups. This finding was comparable with that of Ali et al.[15] Of those 75 patients, 28 suffered from various types of infections at the onset of disease. Urinary tract infection was the commonest (26.2%) in relapse group followed by respiratory tract infections (15.2%) and peritonitis (8.7%). In patients receiving alternate-day prednisone, one nonrandomized trial and two RCTs suggested that the frequency of relapse was reduced if prednisone is administered for 5–7 days at the onset of an upper respiratory infection.[16] However, Biswas BK[7] described that infection is an important cause of relapse and Gulati et al.8 stated that asymptomatic UTI might be an important and under diagnosed cause of relapse.

Conclusion:

Young age at diagnosis of INS, male gender, low serum albumin and infections were predictive risk factors of multiple relapses. So, physicians should be vigilant to monitor these patients closely and counsel the families of nephrotic children regarding the prediction of subsequent relapses and ultimate outcome. 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.

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