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Predictors of Relapse in Children with Steroid-Sensitive Nephrotic Syndrome

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ORIGINAL ARTICLE

ABSTRACT

Objective: The present cohort study was conducted on children with steroid-sensitive nephrotic syndrome to identify the predictors of subsequent relapse in them as well as to determine the predictive score at which a child is at risk of developing the relapse.

Patients & Methods: The study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh and at Bangladesh Institute of Child Health (BICH), Dhaka between January 2011 to December 2011 on 99 consecutive steroid-sensitive nephrotic syndrome children. Any child with steroid-responsive nephrotic syndrome if exhibited ≥ 2 relapses within 6 months of initial response was considered as frequent relapser, while any child if experiences < 2 relapses within the same period was considered as infrequent relapser and if a child did not have any relapse was termed as non-relapser. Of the 99 children, 60 developed relapse and the rest did not. The putative risk factors were then compared between children who relapsed and who did not relapse. The risk factors were then used in combination to calculate the predictive score to assess what predictor variables and at which predictive score the children are at risk of relapse.

Result: The mean age of the children was a little more than 4 years with no significant difference between the relapser and non-relapser (p=0.288). A male preponderance was observed in either group (71.7% vs. 59%, p=0.191). Majority of the children in both relapser and non-relapser groups (80% and 84.6% respectively) responded early to steroid treatment (p=0.561). The incidences of upper respiratory tract infection (URTI) and urinary tract infection (UTI) were significantly higher among those who relapsed after initial response to steroid therapy than their non-relapser counterpart (p=0.006 and p=0.035 respectively). The incidence of atopy was considerably higher in the former group than that in the latter group (19 vs. 9.4%, p=0.369). However, infections did not demonstrate their significant presence among the relapsers at 2nd relapse. Using 3 predictors (like interval between first relapse and early response, number of relapse within 6 months and infection at first relapse) and a total predictive score of 12 with a cut-off point of 5, over three-quarters (76.7%) of the relapser were found to have predictive score of > 5 as opposed to only 2.6% of the non-relapser. The risk of developing relapse was 3.6 times (95% CI=2.3 - 5.7) higher in children who had predictive score > 5 than those who had score 5 or < 5 (p < 0.001). However, using 5 predictor variables in combination (interval between first relapse and early response, number relapse within 6 months of initial response and infection at first relapse, rapidity of early response and sex) and a total score of 16 with a cut-off value of 9, the risk of developing relapse was 2.5 (1.8-3.4) times more among those who had predictive score>9 than those who had score 9 or less (p< 0.001).

Conclusion: The study concludes that the risk of relapse in children with steroid sensitive nephrotic syndrome can be better predicted using a number of predictor variables in combination than the factors in isolation.

Key words: *Steroid-sensitive nephrotic syndrome, predictors of relapse, predictive score.*

INTRODUCTION

Idiopathic nephrotic syndrome (INS) is the most common glomerulopathy in children, with an annual incidence of approximately 2-3 new cases per 100,000 population under the age of 18 years.[1] Its incidence in Asian children is higher (9-16/100000 children) as compared to Western children (2-4/10000 children).[2] Fifty to sixty

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percent of the total admission in the paediatric renal unit of BSMMU Hospital is due to idiopathic nephrotic syndrome indicating that the disease is quite common in children of Bangladesh as well.[3]

Prednisolone is the drug of choice for nephrotic syndrome with 90% of the mesangio capillary nephrotic syndrome respond well to steroid therapy.[4,5] The use of this drug since 1950 has lowered the mortality from 35% to mere 3%.[6] But the problem of relapse remains a great challenge in successful therapy. As long as the child remains steroid sensitive, the renal function remains excellent.[7]

Relapse can be classified into infrequent relapses (< 2 relapses within 6 months of initial attack) and frequent relapses (2 or > 2 relapses within 6 months of initial attack). Three-quarters of the steroid-sensitive nephrotic syndrome will have a subsequent relapse and one-third of them suffer from frequent relapses.[8] The frequency of relapse is also higher in our country.[9] Among the admitted cases of NS at BSMMU, 83% cases were due to relapse and 55% due to frequent relapse NS.[10] Although a great deal of information has been obtained over the past decades on underlying histopathological abnormalities and their relationship with clinical course, the causes of relapse still remain obscured.[11] Very few published studies are available to describe the risk factors for relapse.

Among a number of factors studied, lower age and lower serum total protein were identified as significant risk factors for frequent relapse. Infection, particularly urinary tract infection, and inadequacy of initial therapy were also identified as possible risk factors for relapse.[5,12,13] Attack with common cold also triggers the relapse.[14]

Nephrotic syndrome is a disease of relapse and remission. About two-thirds of the patients experience relapses after the first remission.[15] In spite of that, some children relapse more frequently than do others. Patients with frequent relapses are at risk of severe steroid toxicity, because of the continuous high dose of prednisolone used to induce a remission.[16] Identification of these children, early in the course of the disease, will be helpful in counseling parents, as well as alerting the attending clinician about the need to closely monitor those patients. But no single predictor variable is sufficiently sensitive to predict the cases at risk of relapse. Noer[17] taking 5 predictor variables in combination and using discriminant analyses determined a predictive score for steroid-sensitive nephrotic syndrome cases who are at risk of relapse after initial response.

The present study is, therefore, intended to identify the predictors of relapse as well as to determine the predictive score combining the factors found to be significantly associated with relapse. This will help in identifying potential cases of relapse with fair degree of accuracy.

PATIENTS & METHODS

The study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka and at Bangladesh Institute of Child Health (BICH) Dhaka between January 2011 to December 2011. Children (ranging from 1-18 years) of 1st attack nephrotic syndrome responding to steroid therapy (response within 4 weeks of initial steroid therapy) were considered as the study population. A total of 99 such children were consecutively included in the study. Having obtained ethical clearance from the Institutional Review Board (IRB), BSMMU and BICH, Dhaka and written consent from the respondents (father/mother or legal guardian of the child) data were collected by interview of the respondents and clinical and laboratory examination of the children using a questionnaire covering the key variables of interest.

The clinical features and risk factors recorded as absent or present were white precipitation after boiling of urine, gradual swelling of whole body, burning micturation, scanty micturation, abdominal distention, abdominal pain, scrotal swelling, cough, respiratory difficulty, fever, sore throat, any skin infection and previous hospital admission for same illness. Nephrotic syndrome was ascertained by standard heat coagulation test, serum albumin estimation, spot urinary protein creatinine ratio and total 24-hrs urinary protein estimation. Steroid therapy at first attack was given as Prednisolone 60 mg/m^2/day

(maximum 80 mg/day) in divided doses for 6 weeks followed by a maintenance dose of 40 mg/m^2/ on every alternate day for 6 weeks. After initial response all patients were followed up for 6 months for assessing subsequent relapses (if any). If subsequent relapse occurred, how many relapses occurred and the time interval between initial response and 1st relapse were noted. Children were categorized as frequent relapser (any child with steroid-responsive nephrotic syndrome if exhibited ≥ 2 relapses within 6 months of initial response), infrequent relapser (any child if experiences < 2 relapse within the same period) and non-relapser (if a child did not have any relapse).[18] Of the 99 children, 60 relapsed within the stipulated time period and 39 did not do so. All the suspected risk factors were then compared between children who relapsed and who did not relapse. The risk factors were then used in combination to calculate the predictive score to assess what predictor variables and at which predictive score the children were at risk of relapse.

The biochemical tests like serum albumin, serum cholesterol, serum creatinine, blood urea and 24 hours urinary total protein were measured by autoanalyzer technique (RA-50 chemistry analyzer). Evidence of infections was judged by clinical and/or laboratory tests of specific specimens including blood and urine for culture and X-ray chest in the initial attack and in the subsequent attacks if needed.

Predicting Relapse Using Predictive Score:

In the present study a number of predictor variables were used in combination. The predictive score was calculated according to the study of Noer[17] as shown in table I.

When 3 predictor variables were used in combination, the highest obtainable score was 12 and when 5 variables were used, the highest possible score was 16. The cut-off point for predictive score, when 3 variables were used, was 5, while the cut-point for predictive score, when 5 variables were used, was 9 (table I).

Data were processed and analyzed using SPSS (Statistical Package for Social Sciences) version 11.5. Data presented on categorical scale were compared between groups using Chi-square (χ^2) or Fisher's Exact Probability Test, while the data presented on continuous scale were compared using Student's t-Test. The risk of developing frequent relapse was calculated using Relative Risk (RR) with 95% confidence interval for RR. The level of significance for any analytical tests was set at 0.05 and $p < 0.05$ was considered significant.

TABLE I: Predictive score for relapse in steroid-responsive nephritic syndrome.

Variables	Predictive score 3 variables	5 variables
Interval between first relapse and early response (months)		
< 1	3	3
1 - 3	5	5
> 3	3	3
Number relapse within 6 months of initial response		
< 2	1	1
≥ 2	4	4
Infection at 1st relapse		
Present	3	3
Absent	1	1
Sex		
Male	—	2
Female		1
Rapidity of early steroid response (wks.)		
≤ 4	—	1
> 4		2
Highest possible score	**12**	**16**

RESULT

There was no significant difference between the relapser and non-relapser with respect to age of the children (mean age was > 4 years, p=0.288). Males were predominant in both relapser and non-relapser (71.7% vs. 59%, p=0.191). The mean durations of illness at presentation in relapser and non-relapser were 2.81 and 2.21 weeks respectively (p=0.181) (Table II). Majority of the children in both relapser and non-relapser groups (80% and 84.6% respectively) responded early to steroid treatment (p=0.561). The mean time to relapse after initial response to steroid therapy was 14.9 weeks and the shortest and the longest time required to first relapse were

1 and 50 weeks respectively. Number of relapses within 6 months of initial response was 2.4 and the lowest and the highest numbers were 2 and 4 respectively. Of the relapsers 53% had frequent relapse (≥ 2 relapse within 6 months of initial response) and 47% infrequent relapse (< 2 relapse within 6 months of initial response).

TABLE I : Demographic characteristics between groups.

Demographic characteristics	Outcome		p-value
	Relapser (n = 60)	Non-relapser (n = 39)	
Age# (yrs)	4.12±3.14	4.80±3.60	0.288
Sex*			
Male	43(71.7)	23(59.0)	0.191
Female	17(28.3)	16(41.0)	
Duration of illness# (weeks)	2.81±2.44	2.21±1.74	0.181

*Figures in the parenthesis denote corresponding %; *χ^2 Test was employed to analyse the data.*
#Data were analysed using Unpaired t-Test and were presented as mean±SD.

At initial attack, a significantly higher proportion of relapsers had upper respiratory tract and urinary tract infections than those in the non-relapsers (p=0.048 and p=0.045 respectively) (table III). The incidences of upper respiratory tract infection (URTI) and urinary tract infection (UTI) were significantly higher among those who exhibited 1st relapse after initial response to steroid therapy than their non-relapser counterpart (p=0.006 and p=0.035 respectively). The incidence of atopy was considerably higher in the former group than that in the latter group (19 vs. 9.4%, p = 0.369) (table IV). However, none of the five infections like (Lower respiratory tract infection) URTI, LRTI, UTI, gastrointestinal infections and soft tissue infections demonstrated their significant presence among the relapsers at 2nd relapse. Only 7 patients among the relapser groups attended with 3rd relapse. The rest of the relapsers and none of the non-relapsers could not be traced. Of the 7 patients who presented with 3rd relapse, 4(57.1%) suffered from URTI, LRTI, UTI and atopy each was found in 2 cases.

TABLE II : Comparison of different types of infections at presentation between groups.

Infection	Outcome		p-value
	Relapser (n = 60)	Non-relapser (n = 39)	
URTI	23(38.3)	8(20.5)	0.048
LRTI	5(8.3)	6(15.4)	0.191
Gastrointestinal infection	6(10.0)	5(12.8)	0.663
Soft tissue infection	5(8.3)	1(2.6)	0.398
Urinary tract infection	13(21.7)	3(7.7)	0.045
Atopy	15(25.0)	9(23.1)	0.827

*Figures in the parenthesis denote corresponding %; *χ^2 Test was employed to analyse the data.*

TABLE IV : Association of infections and atopy with 1st relapse.

Variables	Group		p-value
	Relapser (n=58)	Non-relapser (n=32)	
URTI*	32(55.2)	8(25.0)	0.006
LRTI#	4(6.9)	1(3.1)	0.366
UTI*	19(32.8)	4(12.8)	0.035
Gastrointestinal infection#	3(5.2)	3(9.4)	0.361
Soft tissue infection#	4(6.9)	2(6.3)	0.639
Atopy*	11(19.0)	3(9.4)	0.369

Figures in the parenthesis denote corresponding %;χ^2 *Test was done to analyse the data;*
#Fisher's Exact Test was employed to analyse the data

Using 3 predictors (like interval between first relapse and early response, number relapse within 6 months and infection at first relapse) and a total predictive score of 12 with a cut-off point of 5, more than three-quarter (76.7%) of the relapser were found to have predictive score of > 5 as opposed to only 2.6% of the non-relapser. The risk of developing relapse was estimated to be 3.6-fold (95% CI=2.3-5.7) higher in children who had predictive score of > 5 than those who had score of 5 or < 5 (p < 0.001) (Table V). However, using 5 predictor variables in combination (interval between first relapse and early response, number relapse within 6 months of initial response and infection at first relapse, rapidity of early response and sex) and a total score of 16 with a cut-off value of 9, the risk of developing relapse was calculated to be 2.5 (1.8-3.4) times higher among those who had predictive score of > 9 than those who had score of 9 or less (p < 0.001) (table VI).

TABLE V : Estimation of risk of relapse using predictive score by 3 variables.

Predictive score	Group		RR	p-value
	Relapser (n = 60)	Non-relapser (n = 39)	(95% CI of RR)	
> 5	46(76.7)	1(2.6)	3.6 (2.3-5.7)	< 0.001
≤ 5	14(23.3)	38(97.4)		

Figures in the parentheses denote corresponding %; Data were analysed using χ^2 Test.

TABLE VI : Estimation of risk of relapse using predictive score by 5 variables.

Predictive score	Group		RR	p-value
	Relapser (n = 60)	Non-relapser (n = 39)	(95% CI of RR)	
> 9	36(60.0)	1(2.6)	2.5 (1.8-3.4)	< 0.001
≤ 9	24(40.0)	38(97.4)		

Figures in the parentheses denote corresponding %; Data were analysed using χ^2 Test.

DISCUSSION

Relapse is a common phenomenon in children who once suffered from nephrotic syndrome. Researches have mainly focused on underlying histopathological abnormalities and their relationship with clinical course and as such the causes of relapse remain obscured.[11] Limited studies are available to describe the risk factors for frequent relapse NS in children.

The present study aimed at finding the predictors of relapse in children with steroid-sensitive nephritic syndrome demonstrated that age distribution of the relapsers and non-relapsers was almost comparable with mean ages of children of the former and the latter groups being 4.1 and 4.8 years respectively. Majority of the children in either group was male. A significantly higher proportion of children among the relapsers presented with upper respiratory tract and urinary tract infection at initial attack than those among the non-relapsers. Several studies reported that lower age and lower serum total protein at onset, infection, particularly urinary infection and inadequacy of initial therapy as determinants for relapse[5,12-14,19] although in the present study age was not found as a predictor of relapse.

In a study conducted in Indonesia, five variables were identified as the predictors of relapse. They were rapidity of response to steroid therapy at first attack, number of relapse within first 6 months after the initial response, infection, hematuria and male gender. As there were a number of factors implicated with relapse, they used them in combination to predict the cases of nephrotic syndrome at risk of relapse after initial response. Accordingly when they used all the 5 parameters together and a total score of 16 with a cut-off point of 9, they found that the children with a composite score of > 9 were more likely to be frequent relapser than those who had score of 9 or < 9. However, when 3 parameters (interval between first relapse and early response, number relapse within 6 months and infection at first relapse) and a total score of 12 with a cut-off value of 5 were used, an even higher number of children with predictive score of > 5 were correctly predicted to be at risk of relapse. These findings are almost consistent with findings of the present study. In the present study it was found that a child with a predictive score of > 5 will carry 3.6 times higher risk of developing relapse than when the child with a predictive score of 5 or less than 5 (when 3 predictor variables were used). But when 5 predictor variables were used in combination the relative risk of developing relapse among children with predictive score of > 9 was reduced to 2.5 compared to those with predictive score of 9 or < 9. Thus the data of the present study and those of Noer *et al*[17] suggest that a combination of risk factors predicts risk of relapse in children with steroid-sensitive nephrotic syndrome better than the factors individually do. The data also indicate that the factors that are more frequently associated with relapse should only be taken into account in calculating a predictive score.

The most important factor that determines prognosis in children with nephrotic syndrome is steroid responsiveness. While more than 70 per cent of children with steroid-sensitive nephrotic syndrome relapse and almost 50 per cent have frequent relapses or steroid dependence, their risk of progression to chronic renal failure is minimal. Studies on natural history show that 15-25 per cent patients may continue to have

relapses 10-15 yr after the onset of the disease. As, frequent relapses during childhood is associated with relapses in adulthood as well,[20] early identification of children at risk of frequent relapse is badly needed.

The study concludes that the presence of upper respiratory tract and urinary tract infections and atopy at the initial attack of steroid-sensitive nephrotic syndrome are the predictors of subsequent relapse. However, the risk of relapse in children with steroid sensitive nephrotic syndrome can be better predicted using a number of predictor variables in combination than the factors used alone. The data generated from the study is thought to be of immense clinical significance in identifying children at risk of relapse nephrotic syndrome, early in the course of the disease.

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