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Original Article

Predictors of frequent relapsing and steroid-dependent nephrotic syndrome in children

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Abstract

Aim: To determine the predictors of frequent relapses and steroid dependency in children with steroid-sensitive nephrotic syndrome.

Material and Methods: All children aged six months to 18 years with steroid-sensitive nephrotic syndrome registered in the nephrology clinic between 2003 and 2015 at a tertiary center who were followed up for at least 1year after onset were included in the study.

Results: Two hundred seventy-seven patients with steroid-sensitive nephrotic syndrome who were followed up for at least 1 year from onset of disease were included. There were 157 infrequent relapsers and 120 frequent relapsers (frequent relapses and or steroid-dependent). Compared with infrequent relapsers, frequent relapsers had a significantly lower age at onset (51.53±40.42 vs. 61.97±40.66 months; p=0.035), lesser time to first relapse (time from the start of initial treatment to first relapse (8.65±11.99 vs. 23.46±24.05 months; p<0.001) and a higher number of relapses with infection (8.65±11.99 vs. 1.25±1.85; p<0.001). On multivariate logistic regression analysis, time to first relapse less than six months [OR: 3.93; 95% CI: (1.97- 7.82)] and concomitant infection during relapses [OR: 1.82; 95% CI:(1.56-2.14)] were significant predictors of frequent relapses, and males were less likely to become frequent relapsers [OR: 0.48; 95% CI:(0.24-0.93)]. Kaplan-Meier analysis and the log-rank test also showed that a first relapse within six months was associated with frequent relapses. Age at onset and inadequate steroid therapy at onset did not determine frequent relapses.

Conclusion: Shorter time to first relapse and concomitant infection during relapses can predict future frequent relapses. These predictors may be useful to counsel patients, to follow them up more closely, and to develop better treatment protocols and relapse-specific interventions.

Keywords: Frequent relapses, nephrotic syndrome, steroid dependent, predictors

Introduction

Idiopathic nephrotic syndrome is the most common glomerular disease in childhood with an incidence of 2-3 per 100,000 children. The majority of children have steroid-sensitive nephrotic syndrome (SSNS). Although SSNS has a favorable long-term outcome, about half of all patients with SSNS become frequent relapsers and or steroid dependent and may experience several adverse effects secondary to the disease or its treatment (1). Until the prevention of frequent relapse occurrence is possible, finding the safest and most effective protocols to treat such patients thus remain the major unsolved problems in the management of children with SSNS. The first step in this direction would be to identify risk factors for frequent relapses.

Several studies have attempted to identify the patient characteristics associated with a high risk of frequent relapses and or steroid-dependent nephrotic syndrome; however, the results have been conflicting (3-17).

The aim of this study was to determine the clinical characteristics that correlate with frequent relapses or steroid dependency

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Material and Methods

This retrospective and prospective analytical study was conducted at a nephrology clinic in a tertiary care center after obtaining approval from the institutional ethics committee prior to starting the study (ref no BMCRI/PS/344/2015-16). Written informed consent was obtained from the parents/guardians of the patients.

All children aged 6 months to 18 years with SSNS registered in our nephrology clinic between 2003 and 2015 at onset of disease and who were followed up by us for at least 1year from onset of disease were included in the study. Children who had less than 12 months follow-up, those who were registered sometime after the onset of disease, and those who had congenital, secondary or steroid-resistant nephrotic syndrome (SRNS) were excluded.

Data were collected from individual patients' standardized files maintained at the nephrology clinic and were recorded in a structured pretested proforma. Missing data were collected during follow-up and over the telephone.

Definitions: Diagnosis and treatment of nephrotic syndrome were as per the standard protocol of the Indian Society of Paediatric Nephrology.

Nephrotic syndrome is characterized by heavy proteinuria (urine albumin 3+ or 4+ or proteinuria >40 mg/m^2/h), hypoalbuminemia (serum albumin <2.5 gm/dL), hyperlipidemia (serum cholesterol >200 mg/dL), and edema

Remission: Urine albumin nil or trace (or proteinuria <4 mg/m2/h) for 3 consecutive early morning specimens.

Relapse: Urine albumin 3+ or 4+ (or proteinuria >40 mg/m^2/h) for 3 consecutive early morning specimens, having been in remission previously.

Frequent relapses: Two or more relapses in the initial six months or more than three relapses in any twelve months.

Steroid dependence: Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.

Steroid resistance: Absence of remission despite therapy with daily prednisolone at a dosage of 2 mg/kg per day for 4 weeks.

Treatment regimens: the initial episode of nephrotic syndrome has been treated differently over the years. Children with onset before 2003 were treated with regimen A [4 weeks daily (2 mg/kg/day) followed by 4 weeks alternate day treatment (1.5mg/kg/day)]. From 2003 to 2008, the initial episode was treated with regimen B [6 weeks (2mg/kg/day) followed by 6 weeks of alternate day therapy (1.5 mg/kg/day)]. From 2008 onwards, the initial episode was treated alternately with regimen B or regimen C [6 weeks daily (2mg/kg/day) followed by 6 weeks alternate day treatment (1.5mg/kg/day), followed by tapering of alternate day steroids over 12 weeks]. Relapses were treated with 2 weeks (2 mg/kg/day) daily regimen followed by 4 weeks (1.5mg/kg/day) alternate day treatment.

The following variables were considered as potential risk factors/predictors of frequent relapses based on previous studies: age at onset, sex, inadequate steroid therapy (less than 8 weeks) at onset, time of first relapse (time from the start of initial treatment to first relapse), and concurrent infections during relapses.

Statistical analysis

The associations between potential risk factors among infrequent and frequent relapsers (frequent relapses and or steroid dependence) were studied initially through a univariate analysis. Results of continuous measurements are presented as mean±SD (min-max) and results of categorical measurements are presented as percentages (%). Means were compared using Student's t-test (two tailed, independent). Categorical variables were assessed using the Chi-square/Fisher's exact test. Logistic regression analysis was employed to examine the independent effect of related risk factors on relapses; adjusted odds ratio (AOR) =1, no relationship, AOR >1, positive association and AOR <1: negative association.

Statistical tests were performed at a 5% level of significance.

Statistical software, SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0, and R environment ver.2.11.1 were used for the analysis of the data.

Results

Among 578 children with nephrotic syndrome registered in our nephrology clinic, 71 with SRNS, 2 with congenital nephrotic syndrome, and 1 with secondary nephrotic syndrome were excluded. Among the remaining 504 children with SSNS, 126 patients who were registered after onset and 101 patients were followed up for less than 1 year were excluded. The remaining 277 patients with SSNS who were followed up for at least 1 year from onset of disease were included in the study.

Among the 277 included children, 157 (56.6%) had infrequent relapses and 120 (43.3%) had frequent relapses and or steroid dependence (Figure1). The mean duration of follow-up of the included children was 4.61±3.23 years. Their characteristics are shown in Table1. Frequent relapsers (frequent relapses and or steroid dependence) had a significantly lower age at onset (61.97±40.66 vs. 51.53±40.42 months, p=0.035), shorter time to first relapse (8.65±11.99 vs. 23.46±24.05 months, p<0.001) when compared with infrequent relapsers. There was no significant difference between the two groups with respect to sex ratio, hypertension at onset, serum albumin at onset, serum creatinine at onset, the proportion of children who received inadequate therapy at onset, time to response to steroid at the first episode.

Three children had onset of nephrotic syndrome at less than 1year of age, among whom two became frequent relapsers and one became an infrequent relapser. No biopsy was performed in any of these children. Four children had microscopic hematuria at onset, one of whom also had gross hematuria, and all became frequent relapsers (p=0.034).

Kaplan-Meier analysis and the log-rank test also showed that the first relapse was significantly earlier in the frequent relapsers than in the infrequent relapsers (Figure 2).

Infrequent relapsers had 274 relapses and frequent relapsers had 1171 relapses; 64.35% of relapses had concurrent infections (e.g., upper respiratory tract infections, gastroenteritis, urinary tract infections, acute lower respiratory tract infections, peritonitis). The mean number of relapses with infection was significantly higher in frequent relapsers when compared with infrequent relapsers (9.76 ±7.02 vs 1.75±2.44, p<0.001).

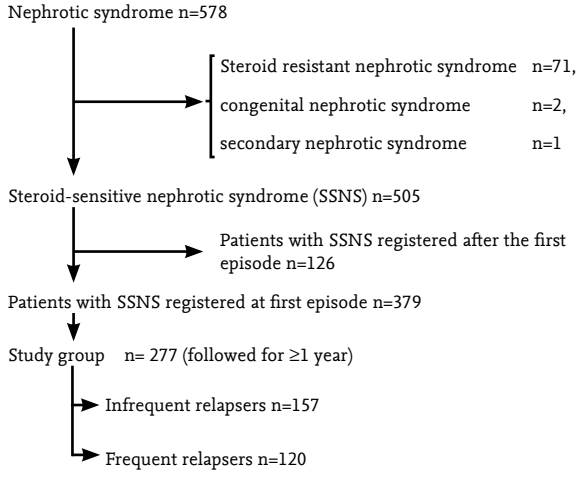


Figure 1. Flow chart of the patients in this study

Table 1. Characteristics of infrequent relapsers and frequent relapsers

	Infrequent relapsers n=157	Frequent relapsers n=120	p
Males n (%)	100 (63.7%)	66 (55%)	0.143[b]
Age at onset in months mean±SD	61.97±40.66	51.53±40.42	0.035[a]
Hematuria at onset n (%)	0	4(3.33%)	0.034[c]
Hypertension at onset n (%)	2 (1.27%)	0	0.507[c]
Serum albumin at onset (g/dL) mean±SD	1.8±0.53	1.8±0.58	0.538[a]
Serum cholesterol at onset (mg/dL) mean±SD	370±125.81	369±115.25	0.564[a]
Serum creatinine at onset (mg/dL) mean±SD	0.6±0.37	0.6±0.31	0.655[a]
Adequate therapy at onset (>8 weeks) n (%)	149 (94%)	112 (93%)	
Inadequate therapy at onset (<8 weeks) n (%)	8 (5.1%)	8 (6.7%)	0.579[b]
Time to remission in first episode (Days) mean±SD	7±5.16	9±6.4	0.082[a]
Time to first relapse (months) Mean±SD	23.46±24.05	8.65±11.99	<0.001[a]
No. of relapses	274	1171	
No. of relapses with infection mean±SD	1.25±1.85	6.11±4.63	<0.001[a]

[a]Student's t-test, [b]Chi square test, [c]Fischer's exact test

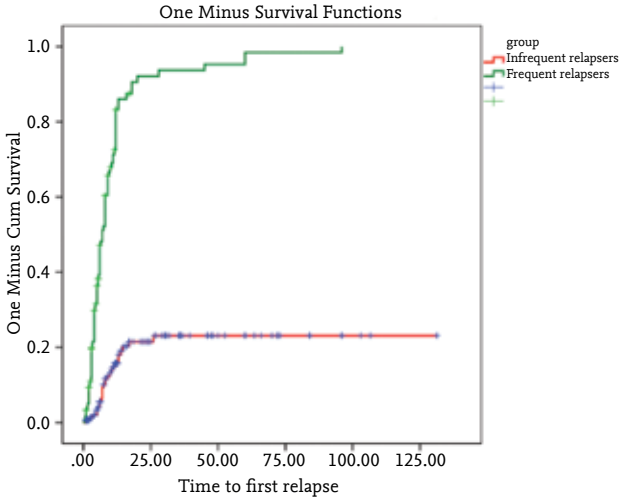
Table 2 presents the logistic regression analysis of factors associated with frequent relapses. Short time to first relapse (<6 months) and concomitant infection during relapses were significantly associated with increased risk of frequent relapses. Patients with a time to first relapse of less than 6 months were 3.93 times more likely to become frequent relapsers [95% confidence interval (CI):(1.97-7.82)]. Patients with concomitant infections during relapses were 1.82 times more likely to become frequent relapsers [95% CI:(1.56-2.14)]. Males were 0.48 times less likely to become frequent relapsers [95% CI:(0.24-0.93)].

Discussion

About 43.3% of children with SSNS in our study became frequent relapsers and or steroid dependent (FR/SD) .The proportion of FR/SD in patients with SSNS followed up from onset of disease varies from 22-61% in previous studies (2-4, 6, 7, 9, 12-14). Such wide variation may be due to different steroid regimens used or biologic variation in disease severity or increased infection-induced relapses.

The first main finding of our study was that short time to first relapse (<6 months) was a predictor of frequent relapse and SDNS, similar to all previous studies (3, 4, 6, 7, 11). Univariate, logistic regression, and Kaplan-Meier analyses showed that time to first relapse was a significant risk factor for FR/SD course.

The second main finding of our study was the significant association of concomitant infection during relapses and frequent relapsers. Concurrent upper respiratory infection during relapse is a risk factor for FR/SD as per a few studies (11, 12, 18). Relapses of nephrotic syndrome often follow minor infections of the upper respiratory or gastrointestinal tracts (19, 20). The mechanism by which infections result in relapses is not clear, but might be related to the upregulation of T cells and cytokine-mediated increase in proteinuria (21, 22). It has been reported recently that small daily doses of prednisolone during infectious illness were effective in reducing infection-associated relapses in frequently relapsing nephrotic syndrome (23). On the contrary, despite using stress dose daily steroid during infections in all our patients, the number of infection-associated relapses was more in frequent relapsers. Frequent relapsers are probably more immunosuppressed either due to the disease or its treatment, and hence are more prone to infection-associated relapses. Prevention of infections with influenza, pneumococcal, and HiB vaccines may reduce the relapses. The majority of our patients could not afford these vaccines. Further studies are needed to determine whether these vaccines can become effective relapse-specific interventions.



	Mean time to first relapse			
	Estimate	SE	95%CI: Lower	95%CI: Upper
Infrequent relapsers	103.30	4.91	93.69	112.92
Frequent relapsers	11.27	1.76	7.82	14.72

χ_2=151.833 (Log-rank test); p<0.001

Figure 2. Kaplan-Meier function analysis of time to first relapse in relation to frequent/infrequent relapses

Table 2. Multivariate Logistic regression analysis to assess the risk factors of frequent relapse nephrotic syndrome

Variables	Logit coefficient	SE	Wald	P value	AOR[a]	95%CI
Age at onset less than 4 years	-0.17	0.35	0.24	0.624	0.84	0.42-1.68
Sex: male	-0.74	0.34	4.69	0.030	0.48	0.24-0.93
Inadequate therapy	-0.30	0.65	0.22	0.640	0.74	0.21-2.64
Time to first relapse <6 months	1.37	0.35	15.17	<0.001	3.93	1.97-7.82
Concomitant infection during relapses	0.60	0.08	55.62	<0.001	1.82	1.56-2.14

[a]Adjusted odds ratio

A few previous studies reported male sex as a risk factor for FR (3,9); however, many other studies showed that male sex did not predict FR (4, 6, 7, 10-12). In contrast, for the first time, our study has identified male sex has having less risk for frequent relapses This may be due to the overall male preponderance in nephrotic syndrome. Our study did not identify young age at onset as a predictor for frequent relapses, in keeping with some studies (4, 5, 7, 8, 10-13, 15), but not with other studies (3, 6, 9, 14). Such conflicting results may be due to differences in patient selection. Low serum albumin at onset has been reported as a risk factor for frequent relapses, as per one previous study (16). We did not identify it as a risk factor, similar to some studies (4, 6, 9).

Many previous studies reported no association between hematuria at first episode and frequent relapses (9, 11-13, 15). One study reported that mean urine red blood cells was higher in frequent relapsers (16). Another recent study reported hematuria at onset as a risk factor for frequent relapses (17). In our study, only four children had microscopic hematuria at onset, but all developed frequent relapses. This number was too small to analyze the statistical significance.

Many previous studies found that time taken to achieve remission at onset was significantly more in frequent relapsers (4, 5, 7, 8, 10, 12, 17). It is possible that frequent relapsers are more immunologically affected hence need prolonged-duration steroid treatment to achieve remission. However, in one of these studies, the Arnold regimen was used, which reduces the steroid dose after 10 days leading to prolongation of the time needed to achieve remission. We are unable to confirm this. The reason for this is not clear. It may be due to ethnic or racial characteristics of the individual patient. Like us, a few other studies also reported no correlation between time to remission and frequent relapses (9, 11).

Adequate initial therapy (at least 8 weeks) with corticosteroids reduces the risk of subsequent relapses. A recent Cochrane review emphasized that prolongation of steroid therapy beyond 2 or 3 months for the treatment of the initial episode of nephrotic syndrome does not reduce the risk of relapses (24). As very few patients received inadequate (less than 8 weeks) initial treatment, we could not analyze whether inadequate therapy was associated with frequent relapses/steroid dependency. Other reported risk factors for frequent relapses, but not evaluated in our study, include the need of methyl prednisolone to achieve remission (5, 10), low immunoglobulin G (25), and high levels of advanced oxidation protein products (AOPP) in the plasma (26).

The strength of our study is in its large sample size with adequate statistical power to identify risk factors. With the exception of two studies (4, 6), all previous research was conducted with small sample sizes.

The limitations of our study include its retrospective nature and inclusion of referred and hospitalized children. However, our aim was to predict the occurrence of FR/SD in children followed up from onset of disease. All patients included in this study had been followed up regularly from onset of disease for at least one year.

In conclusion, we identified shorter time to first relapse and concomitant infection during relapse as risk factors for frequent relapses, and that male sex has a lesser risk of frequent relapses. This will alert physicians to monitor these patients closely and to counsel their families regarding the further course and treatment of disease. This could also be used to determine enrolment into trials to devise better treatment protocols and to develop relapse-specific interventions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of The Bangalore Medical College and Research Institute (Ref. no:BMCRI/PS/344/2015-16).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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R.P.; Writing - B.D., M.L., R.P.; Critical Review - B.D., M.L., R.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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