

Relapses in Children with Steroid-Sensitive Nephrotic Syndrome and Their Predictive Factors

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Abstract

Background: Frequent relapses (FR) are a common occurrence in patients with steroid-sensitive nephrotic syndrome (SSNS). FRs are regarded as one of the key issues because they are linked to high prevalence of sequelae. The objective of our study was to assess the various variables that might be connected to the occurrence of relapse in SSNS.

Methods: 80 children with SSNS were treated from January 2022 to December 2022 in the department of Pediatrics at Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar. Two categories of study participants were created: FR and infrequent relapses (IFR). The study participants ranged in age from one to fourteen years; 45 individuals had FR (56.3%) and 35 had IFR (43.7%). 55 patients (68.7%) were male, while 25 (31.3%) were female.

Results: The prevalence of FR was higher in children living in urban areas and was high across all age categories, with the exception of those aged 1 to 5 years. Regarding age, gender, location of residence, and renal functioning, there was no discernible difference between the two groups. The presence of hematuria, the duration of treatment to respond, and the dose of steroid required were all significantly higher in the FR group.

Conclusion: With knowledge of predictors of relapses in SSNS, clinicians can easily spot potential FR and monitor them closely.

Keywords: Relapses, SSNS, IFR, FR.

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Introduction

Nephrotic syndrome (NS), which is 15 times more frequent in children than in adults, is largely a paediatric illness. According to reports, NS affects 2-3/100,000 children

annually. [1] Heavy proteinuria (>3.5g/24h in adults, 40mg/m²/h in children), hypoalbuminemia (<=2.5 g/dL), edema, and hyperlipidemia (cholesterol>200mg/dl) are

its defining features. Idiopathic, Secondary and Hereditary are the three subtypes of NS [2-5].

Most of the children who are affected, have steroid-sensitive minimal change disease (MCD). Those who do not respond to steroids are advised to have a renal biopsy [3,6].

Most children with NS relapse within the first six months of starting treatment. 30% of children only have one attack and are cured after taking just one regimen of steroids. The male to female ratio is 2:1 [7]. The peak age of onset of NS is between 18 months and six years.

This study incorporated demographic variables such as age, gender, and place of residence as predictors of the incidence of relapses in SSNS in order to ascertain the prevalence of relapses in children with steroid sensitive NS (SSNS). We also wanted to investigate the connection between the presence of hematuria and renal function at the time of initial presentation and the occurrence of relapses in SSNS, as well as the connection between how quickly an initial attack responded to steroid therapy and how long it lasted, and the occurrence of subsequent relapses in SSNS.

Material and Methods

From January 2022 to December 2022, this study was carried out in the Department of Pediatrics, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar. 80 patients with SSNS in all, ranging in age from one to 14 years, were identified, treated, and monitored. When older children with collected 24-hour urine met the following criteria, the diagnosis of NS was made: heavy proteinuria >40 mg/m²/h; protein/creatinine ratio >2 ; Albustix +++ or high; hypoalbuminemia ≤ 2.5 g/dL; or edema and hyperlipidemia with total cholesterol >200 mg/dL. [1-3]

Those who experienced a complete remission with steroid medication for four weeks were considered to have steroid-responsive NS. Failure to attain remission after four weeks of treatment with prednisone 60 mg/m² was used to identify steroid-resistant NS. The presence of at least five red blood cells per microliter of urine is referred to as hematuria.

Reference ranges for serum creatinine and blood urea for children and adolescents were 0.3–0.7 mg/dL and 40 mg/dL, respectively.

The Pediatric Unit administered care in accordance with the International Society for Kidney Disease in Children's protocol (ISKDC). Prednisone 60 mg/m²/day or 2mg/kg/day in divided doses was administered for four weeks followed by prednisone 40mg/m²/day or 1.5mg/kg/day for additional four weeks alternate-day in divided doses for the initial attack. After four additional weeks of alternate-day therapy, the intensity was decreased. Relapse was treated with prednisone in a dose of 60 mg/m²/day, until 3 consecutive early morning urine sample became protein free, followed by alternate-day prednisone 40mg/m² for four weeks.

Age at presentation, gender, place of residency, hematuria at initial presentation, renal function (B. urea, S. creatinine), time to response to steroid medication, duration of steroid therapy, and number of relapses were all gathered from the patient record files.

Patients having inadequate data at initial presentation, those who had been followed for less than 12 months, those with steroid-resistant NS, and those with congenital NS were all excluded from the study.

Accordingly, the study patients were divided into two groups:

- a) Infrequent relapses (IFR): less than two relapses within the first six months of treatment or less than four relapses in any subsequent year.

b) Frequent relapses (FR): two or more relapses within six months after the initial therapy, or four or more in a year.

Patients with FR and IFR were compared in terms of age and sex, place of residence, presence of hematuria, renal function (B. urea and S. creatinine), time to response to steroid medication, and length of maintenance steroid therapy while analysing the data. Using the most recent version of statistical software, SPSS 24.0, data was collected and analysed. The Chi-square test is used to provide the data as straightforward percentages or numbers. The number and percentage with usage of probability value are offered for testing the statistical significance of difference between the various parameters. P-values <0.05 were statistically significant.

Results

This study comprised a total of 80 kids with SSNS. 35 of them had IFR (43.7%) and 45 of

them had FR (56.3%). The male to female ratio was 2.2:1, with 55 patients (68.7%) being male and 25 patients (31.3%) being female. 51 individuals (63.7%) in the most prevalent age group at presentation, 1 to 5 years, were included in this cohort. The follow-up period lasted between 12 and 72 months, with a mean of 24.7 ± 13.79 months (SD).

Females had a higher incidence of FR than males did, albeit the difference was not statistically significant (P-value = 0.104). All age groups had a high incidence of FR, with the exception of those 1 to 5 years old, where there were 24 IFR (68.6%) and 27 FR (60%) although the difference was not statistically significant (P-value = 0.708).

Children who lived in urban areas were more likely to have FR (n = 24, 53.3%) than those who lived in rural areas (n = 21, 46.7%); nevertheless, there was no statistically significant difference between the two groups (P-value = 0.734). [Table 1].

Table 1: Correlation of relapses in children with nephrotic syndrome by gender, age and place of residence

	Study groups	
	Infrequent relapse(n=35)	Frequent relapse(n=45)
Gender	No. (%)	No. (%)
Male	28 (80)	27 (60.0)
Female	7 (20)	18 (40.0)
P-value	0.104	
Age-groups	No. (%)	No. (%)
1–5years	24 (68.6)	27 (60.0)
>5–10years	9 (25.7)	14 (31.1)
>10years	2 (5.7)	4 (8.9)
P-value	0.708	
Placeofresidence	No. (%)	No. (%)
Rural	15 (42.9)	21 (46.7)
Urban	20 (57.1)	24 (53.3)
P-value	0.734	

15 patients in all had hematuria; of these, 13 (28.9%) had FR and two (5.7%) had IFR. Statistics showed that the difference was significant (P-value = 0.008; Table 2).

Table 2: Correlation of relapse in patients with nephrotic syndrome with the presence of hematuria at onset

	Study groups	
	Infrequent relapse(n=35)	Frequent relapse(n=45)
Hematuria	No. (%)	No. (%)
Yes	2 (5.7)	13 (28.9)
No	33 (94.3)	32 (71.1)
<i>P</i> -value	0.008	

The majority of IFR patients (n = 33, 94.3%) responded to steroid medication in under two weeks, while the majority of FR patients (n = 23, 51.1%) responded to steroid therapy in between two and four weeks. With a *P*-value of 0.001, a statistically significant difference was discovered. Whereas patients with FR (n = 12, 26.7%) required medication for longer durations of time, those with IFR (n = 15, 42.9%) required treatment for shorter periods of time (Table 3).

Table 3: Correlation of relapses in patients with nephrotic syndrome with time needed to respond to steroid therapy and duration of maintenance steroid therapy

	Study groups	
	Infrequent relapse(n=35)	Frequent relapse(n=45)
	No. (%)	No. (%)
Time for response		
≤2weeks	33 (94.3)	21 (46.7)
2–4weeks	2 (5.7)	23 (51.1)
4–8weeks	0 (0.0)	1 (2.2)
<i>P</i> -value	0.001	
Duration of treatment		
≤2months	9 (25.7)	15 (33.3)
2–3months	11 (31.4)	18 (40)
3–6months	15 (42.9)	12 (26.7)
<i>P</i> -value	0.392	

The majority of patients in the IFR and FR groups recorded normal values for renal function measures, and Table 4 results between the two groups reveal that there was no statistically significant difference between them.

Table 4: Correlation of relapses in patients with nephrotic syndrome with renal function, blood urea and serum creatinine

	Study groups	
	Infrequent relapse(n=35)	Frequent relapse(n=45)
	No. (%)	No. (%)
Blood urea		
≤40mg/dL	33 (94.3)	42 (93.3)
>40mg/dL	2 (5.7)	3 (6.7)
<i>P</i> -value	0.861	
Serum creatinine		
Normal	34 (97.1)	43 (95.6)
Elevated for age-range	1 (2.9)	2 (4.4)
<i>P</i> -value	0.711	

Discussion

This study findings, which were consistent with other studies, showed that male patients outnumbered female patients. [2,7-13] The most prevalent age range at the presentation was 1 to 5 years old, which was also observed in earlier studies from various regions. [10-14]

In our investigation, 56.3% of the participants had FR, which is greater than the prevalence of IFR (43.7%); Esfahani *et al.*, [7] Anderson *et al.*, [13] Constantinescu *et al.*, [15] and Béatrice *et al.* [17] have all reported data along the same lines. We found no connection between age at presentation and subsequent relapses among patients with NS, which is in line with other research by Constantinescu *et al.*, [15] Shuichiro *et al.*, [17] and Takeda *et al.*, [18]. However, Anderson *et al.* [13] and Sarker *et al.* [19] discovered a strong association between the age at presentation (<4 years and <5 years, respectively) and the likelihood of future relapses.

According to a recent Indian study, FR patients tend to be younger when the disease first manifests, and relapse frequency decreases with age. [20] This disparity may be explained by the racial diversity of the study populations of the various studies as well as the diversity of idiopathic NS patterns among the different ethnic groups. [13]

Gender and FR have been found to be negatively correlated in numerous research. [15,17-20]

Despite the prolonged steroid course, Anderson *et al.* [13] reported that male gender was associated with a higher risk of steroid dependency and FR. A different study discovered that FR is more likely to occur in male. [21]

In our study, patients who resided in urban rather than rural areas were more likely to experience FR. Sarker *et al.* reported a

significantly higher incidence of FR in rural children than in urban children ($P < 0.05$), which is in contrast to this finding. [19] They highlighted the delay in the start of particular treatment in rural locations as their justification for this observation.

The association between hematuria at initial presentation and subsequent relapse was an intriguing finding in our study. Several research showed this connection. In a cohort of 50 children with NS who were >8 years old, Juiwen *et al.* [22] reported a prevalence of hematuria at initial presentation of 28%. Hematuria was independently linked to late steroid resistance, according to a recent Indian study. [20]

A statistically significant correlation between early response to steroid therapy and a higher prevalence of IFR in patients with SSNS was another intriguing finding in this investigation. According to Shuichiro *et al.*, patients who responded to first steroid therapy within eight days had a good clinical course, while those who responded after nine days or more had a steroid-dependent course. [17]

Yap *et al.* brought attention to this fact when they said that in 91 Asian infants with SSNS, the initial duration of remission lasting nine days or more was substantially related with steroid dependence. [23] Moreover, Constantinescu *et al.* noted a propensity for FR or steroid dependence in patients who took longer to react. This was significant only for patients who did not have hematuria, as hematuria was associated with a similar likelihood of IFR or FR/steroid reliance. [15] A longer course of steroid medication was associated with fewer relapses among the patients in two earlier studies by Constantinescu *et al.* [15] and Trompeter *et al.* [24], but these findings were comparable to ours and the results were statistically insignificant. However, Anderson *et al.* [13]

discovered a strong correlation between a prolonged steroid therapy regimen (>12 weeks) and a decrease in the frequency of relapses.

Conclusion

As a result, our research reveals that FR was more frequently recorded than IFR among kids with SSNS; there was a male predominance and the peak age of NS incidence was 1 to 5 years. Early response to steroid therapy had a substantial link with IFR, but the presence of hematuria at initial presentation had a significant correlation with FR. This information will aid in the early detection of children with FR, enabling appropriate management.

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