

## A Study On Risk Factors of Relapses of Nephrotic Syndrome Among Pediatric Patients At A Tertiary Care Center of Bihar

Ramjee Prasad Gupta<sup>1</sup>, Ranjit Kumar<sup>2\*</sup>, Sneha Jaiswal<sup>3</sup>, Binod Kumar Singh<sup>4</sup>, Akhilesh Kumar<sup>5</sup>

<sup>1</sup>Associate Professor, Department of Pediatrics, NMCH, Patna, Bihar, India

<sup>2</sup>Senior Resident, Department of Pediatrics, NMCH, Patna, Bihar, India

<sup>3</sup>Senior Resident, Department of Physiology, IGIMS, Patna, Bihar, India

<sup>4</sup>Professor, Department of Pediatrics, NMCH, Patna, Bihar, India

<sup>5</sup>Associate Professor, Department of Pediatrics, NMCH, Patna, Bihar, India

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### Abstract

**Introduction:** Nephrotic syndrome (NS) is 15 times more common in children than in adults. NS affects 13/100,000 children <16 years of age. Two-thirds of childhood NS present before the age of 6 years. Therefore, we planned this study with an objective to identify the risk factors for FR in childhood steroid sensitive NS (SSNS). **Methodology:** A prospective study was conducted by the Department of Pediatrics, Nalanda Medical College & Hospital, Bihar, between February 2020 to January 2021. Cases with the first episode of idiopathic SSNS in the age group of 9 months - 12 years, who followed up for at least 12 months were enrolled in the study. NS was diagnosed in accordance with standard criteria. **Results:** A total of 100 children with NS were included in the current study based on inclusion criteria during the study period. There was a male preponderance among the study participants. Incidence of infection and hypertension was 34% and 37%, respectively. Incidence of FR was high in 1-8 years age group. The incidence of FR was less in males than in females; but it was not significant. Majority of the children with IFR group responded to steroid therapy in <2 weeks, while the most children with FR showed response after 3-4 weeks. **Conclusion:** Relapse within first 6 months, associated infections and hypertension were the factors significantly associated with FRs in childhood SSNS. These factors should be kept in mind and should be well documented at the time of initial presentation of NS for the long-term management.

**Keywords:** Risk Factors, Relapses, Nephrotic Syndrome

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### Introduction

Nephrotic syndrome (NS) is 15 times more common in children than in adults. NS affects 13/100,000 children <16 years of age [1,2]. As defined by the International Study of Kidney Disease in Children (ISKDC), NS is characterized by proteinuria (>40 mg/m<sup>2</sup>/h), hypoalbuminemia (<2.5 g/dL), edema, and usually hypercholesterolemia >200 mg/dL [1-3]. Two-thirds of childhood NS present before the age of 6 years. The ratio of boys to girls is 2:1. By late adolescence, both sexes are equally affected. 90% of childhood cases are not associated with any systemic disease and is classified as primary NS [3]. Without treatment, NS in children is associated with a high risk of death, most commonly from infections [2]. Fortunately, 80% of the children with idiopathic NS show remission of proteinuria following treatment with corticosteroids and are classified as 'steroid sensitive' (SS), and they usually have minimal change disease on histopathology [3]. However, in some regions, there have been differences to these findings based on the race [4].

Although glucocorticoid therapy is standard therapy for NS, neither the target cell nor the mechanism of action of steroids has been determined [2]. The majority of children with NS relapse within the first 6 months of initial therapy. Relapses are often triggered by the upper respiratory or gastrointestinal infections [2]. Frequent relapses (FRs) are at high risk of developing complications related to steroid therapy as they need repeated courses of steroid for treatment and they are more prone for systemic infections also.

There were studies predicting some factors for relapse in NS [5,6]. If such relapses could be predicted at the onset of disease, it would lead to better long-term management of the disease.

Therefore, we planned this study with an objective to identify the risk factors for FR in childhood steroid sensitive NS (SSNS)

### Methodology

A prospective study was conducted by the Department of Pediatric of the Nalanda Medical College & Hospital, Bihar, between February 2020 to January 2021. Cases with the first episode of idiopathic SSNS in the age group of 9 months - 12 years, who followed up for at least 12 months were enrolled in the study. Children with incomplete data at initial presentation, congenital and secondary forms of NS, <12 months follow-up, or previous treatment with steroids or immunosuppressive agents, and steroid resistant NS were excluded from the study. NS was diagnosed in accordance with standard criteria [3].

### Factors for relapse in nephrotic syndrome

The laboratory evaluation of the child with the first episode of NS included urinalysis, first-morning urine protein. Chest X-ray and Mantoux testing was done to rule out pulmonary infiltrates and ultrasound abdomen to rule out renal anomalies. Urine for protein/albumin was done routinely to assess the treatment response as well as for follow-up. The children were treated as per revised guidelines for the management of SSNS by Indian Pediatric Nephrology Group [7]. Children with the first episode of NS are treated with oral prednisolone 2 mg/kg daily for 6 weeks (60 mg/m<sup>2</sup>/day) followed by 1.5 mg/kg on alternate days for 6 weeks (40 mg/m<sup>2</sup>, another day). At the end of 12 weeks, steroids were stopped, and children are monitored weekly for signs of relapse. Following steroid therapy, children with NS undergo any one of the following responses.

\*Correspondence

Dr. Ranjit Kumar

Senior Resident, Department of Pediatrics, NMCH, Patna, Bihar, India.

E-mail: [ranjit2k1dmch@gmail.com](mailto:ranjit2k1dmch@gmail.com)

**Frequent relapse (FR)**

Two or more relapses in initial 6 months or more than three relapses in any 12 months.

**Infrequent relapse (IFR)**

About <2 relapses within 6 months of the initial response or <4 relapses for any year thereafter.

**Study participants were divided into 2 groups**

(1) FR and (2) IFR. The following factors were studied as possible risk factors for relapse between 2 groups:

- Age at onset,
- sex,
- serum albumin,
- 24 h urine protein,
- azotemia,
- time taken to achieve remission during the first episode,
- duration of interval between remissions and first relapse,
- associated infections and
- hypertension.

The data collected were coded, edited and entered into computer and were analyzed using a statistical software package, SPSS version 16.00. Student's t-test was used to compare the mean values, and Chi-squared test ( $\chi^2$ ) was used to compare the frequencies. For testing the statistical significance of difference between the different parameters, a p value of less than 0.05 was considered as significant. Informed

consent by parents and Institutional Ethical Committee clearance were obtained.

**Results**

A total of 100 children with NS were included in the current study based on inclusion criteria during the study period. There was a male preponderance among the study participants. The mean age of presentation was  $5.4 \pm 3.2$  years. There were 50 children in each group. The mean time taken to achieve remission during the first episode was  $2.4 \pm 1.6$  weeks. The duration of interval between remission and first relapse was  $6.3 \pm 4.1$  months. Mean serum albumin was  $1.9 \pm 0.7$  (mg/dl) and mean 24h urine protein was  $1119.9 \pm 662$  (mg/dl). Incidence of infection and hypertension was 34% and 37%, respectively. Incidence of FR was high in 1-8 years age group. The incidence of FR was less in males than in females; but it was not significant. Majority of the children with IFR group responded to steroid therapy in <2 weeks, while the most children with FR showed response after 3-4 weeks. The time taken to achieve remission during the first episode was  $2.2 \pm 1.2$  weeks for the FR children and for the IFR children; it was  $1.5 \pm 0.5$  weeks. Hence, the children who took more than 14 days to achieve remission during the first episode were affected with FR. Majority of the children in IFR relapsed after 6 months, while in FR group children, majority relapsed before 6 months. Statistically significant difference was seen between the duration of interval between remission and first relapse for the children with FR and IFR.

**Table 1: Factor and their values**

Factor	Number		P value
	IFR	FR	
<b>Age group (years)</b>			
< 1 year	4	1	>0.05
1-8 years	40	43	
>8 years	6	6	
<b>Gender</b>			
Male	31	18	>0.05
<b>Time taken to achieve remission during first episode (weeks)</b>			
1			<0.05
2	34	5	
3	15	3	
4	1	30	
-	-	7	
<b>Duration of interval between remission and first relapse (months)</b>			
0-1	3	5	<0.05
1-6	3	34	
>6	43	11	
<b>Infections</b>			
Present	3	31	<0.05
<b>Hypertension</b>			
Present	2	35	<0.05

**Discussion**

NS generally tends to follow a benign and chronic relapsing course, but a few patients may have serious or fatal complications. Previous studies have shown that around 80-90% of the patients with childhood NS relapse which is consistent with the findings in our study[8,9]. FR children needed prolonged course of steroids, increasing the risk of steroid toxicity. Increased incidence of steroid toxicity also occurs when children require frequent course of prednisolone therapy. This includes, inter alia, cush in goid appearance, behavioral changes, hypertension, obesity, glucose intolerance, cataract, osteopenia, and decreased growth rate[3]. All these complications impact the daily life children with NS. The relapse pattern is thought to be dependent on numerous factors identified by various investigators and includes age at onset, sex and time to remission after first relapse, degree of albuminuria, hypertension, hematuria, infections, and time taken to achieve remission[5-6,9-18]. In our study, age at onset, sex, serum albumin, 24 h urine protein, and azotemia did not influence the frequency of subsequent relapses. More than 14 days to achieve

remission during the first episode, relapse within first 6 months, associated infections and hypertension were significantly associated with FRs in our study. This study showed a predominance of male patients over females, and the result was similar to studies elsewhere[9-11]. The most common age group at presentation was 1-8 years, which was also noticed in the previous studies from different regions[10, 12-14]. Although shown in the previous studies[5,6,10,15-16], we did not find any correlation between age at presentation and future relapses. As in our study, several studies also reported that there was no significant correlation between sex and FR [5,6,10,16,17].

**Conclusion**

Our study suggests that IFRs were more than the FRs with male predominance in children with NS. More than 14 days to achieve remission during the first episode, relapse within first 6 months, associated infections and hypertension were the factors significantly associated with FRs in childhood SSNS. These factors should be kept in mind and should be well documented at the time of initial presentation of NS for the long-term management.

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