Original Article

Risk factors for relapse in childhood steroid sensitive nephrotic syndrome

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ABSTRACT

Background: Nephrotic syndrome (NS) generally tends to follow a benign and chronic relapsing course. Relapses are a major problem in children with steroid sensitive NS (SSNS). **Objective:** To identify the risk factors for frequent relapse (FR) in the first episode childhood SSNS. **Methods:** This prospective study was conducted in the Government Dharmapuri Medical College Hospital, Tamil Nadu, between July 2013 and January 2016. Children aged 9 months - 12 years with a diagnosis of SSNS (first episode) who came for follow-up for at least 12 months in the pediatric nephrology clinic were included. The enrolled cases were divided into 2 groups: (1) frequent relapser (FR) and (2) infrequent relapser (IFR). 9 factors were studied as possible risk factors for relapse. The data collected were analyzed using Chi-square test and Student's t-test. **Results:** Of 160 SSNS children, there were 92 (57.5%) cases of IFR and 68 (42.5%) cases of FR. There were 97 males (60.6%) and 63 females (39.4%) with a male to female ratio of 1.5:1. The mean age of presentation was 4.37±2.32 years. The mean time taken to achieve remission during the first episode was 1.94±1.04 weeks. The interval between remission and first relapse was 5.56±4.51 months. Incidence of infection and hypertension was 31.9% and 37.5%, respectively. Risk factors significantly associated with FR were: Time taken to achieve remission during the first episode (>14 days) ($p<0.0001$), mean duration of interval between remission and first relapse (within 6 months) ($p<0.0001$), associated infections ($p<0.0001$) and hypertension ($p<0.0001$). Age at onset, sex, serum albumin, 24 h urine protein, and azotemia did not influence the FR in our study. **Conclusion:** More than 14 days to achieve remission during the first episode, relapse within first 6 months, associated infections and hypertension were the factors associated with FRs.

Key words: *Nephritic syndrome, Children, Relapse, Steroid sensitive, Risk factors*

Nephrotic syndrome (NS) is 15 times more common in children than in adults. NS affects 1-3/100,000 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^2/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).

METHODS

This prospective study was conducted at Pediatric Nephrology Clinic in the Government Dharmapuri Medical College Hospital, Tamil Nadu, between July 2013 and January 2016. 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].

The laboratory evaluation of the child with the first episode of NS included urinalysis, first-morning urine protein: Creatinine ratio (PCR), complete blood count, blood urea, serum creatinine, electrolytes, and albumin, and serum cholesterol levels. Serum C3 and anti-streptolysin O was done in the presence of microscopic hematuria. 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^2/day) followed by 1.5 mg/kg on alternate days for 6 weeks (40 mg/m^2/every 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 anyone of the following responses.

Remission

It was indicated by the absence of albumin by Albustix on three consecutive early morning urine samples (or proteinuria <4 mg/m^2/h).

Relapse

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

Frequent Relapser (FR)

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

Infrequent Relapser (IFR)

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

Steroid Dependence

Two consecutive relapses during alternate day steroid therapy or within 14 days of stopping steroids.

Steroid Resistant NS

Inability to induce a remission within 4 weeks of a daily dose of 2 mg/kg/day of prednisolone therapy.

Children with SSNS 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 10.00. Student's t-test was used to compare the mean values, and Chi-squared test (χ^2) was used to compare the frequencies. For testing the statistical significance of difference between the different parameters, a $p<0.05$ was considered as significant. Informed consent by parents and Institutional Ethical Committee clearance was obtained.

RESULTS

A total of 178 children with NS were screened for the possible inclusion during the study period. 18 were excluded because 12 of them had no relapse during the 1 year follow-up and 6 were lost to follow-up (4 steroid resistant). There were 97 male children (60.6%), 63 female children (39.4%) with a male to female ratio of 1.5:1. The mean age of presentation was 4.37±2.32 years. There were 92 children with IFR and 68 children with FR (Figure 1). The mean time taken to achieve remission during the first episode is 1.94±1.04 weeks. The duration of interval between remission and first relapse was 5.56±4.51 months. Incidence of infection and hypertension was 31.9% and 37.5%, respectively (Table 1).

Incidence of FR was high in 1-8 years age group. There were 81 IFR (57.45%) and 60 FR (42.55%); however, the correlation was not statistically significant (p=0.4059) (Table 2). The incidence of FR was less in males than in females; but it was not significant (p=0.0609) (Table 2). Majority of the children with IFR 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 2.9±0.81 weeks for the FR children and for the IFR children; it was 1.24±0.48 weeks (p=0.0001) (Table 3). Hence, the children who took more than 14 days to achieve remission during the first episode were affected with FR.

Majority of the children (90%) in IFR relapsed after 6 months, while in FR group children (76%) relapsed before 6 months. Statistically significant (p=0.0001) difference was

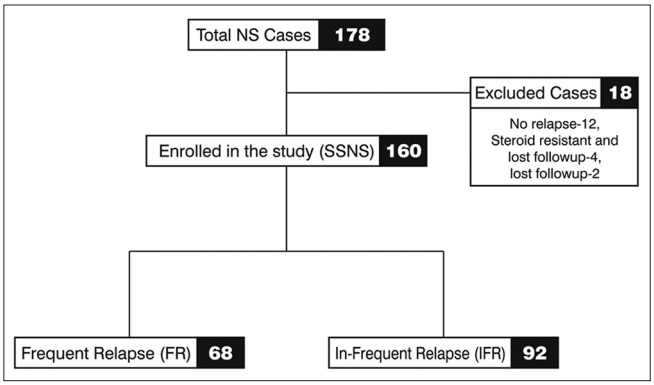

Figure 1: Flow diagram of cases in study

Table 1: Relapse pattern and risk factors in steroid sensitive nephrotic syndrome children (n=160)

Parameters/risk factors	Number of patients (%)/mean±SD
IFR	92 (57.5)
FR	68 (42.5)
Age (years)	4.37±2.32
Male female ratio	1.5:1
Serum albumin (mg/dl)	2.3±0.344
24 h urine protein	1214.8±587
Azotemia	24.07±6.44
Time taken to achieve remission (weeks)	1.94±1.04
Interval between remission and first relapse (months)	5.56±4.51
Mean number of relapses	1.33
Incidence of infection	31.9
Incidence of hypertension	37.5

FR: Frequent relapse, IFR: Infrequent relapse, SD: Standard deviation

Table 2: Correlation of FR with age and sex (n=160)

Factors	n (%)		p value
	IFR	FR	
Age group (years)			
≤1	2 (66.67)	1 (33.33)	0.4059
1-8	81 (57.45)	60 (42.55)	
>8	9 (56.25)	7 (43.75)	
Mean±SD	4.24±2.24	4.5±2.4	
Sex			
Male	62 (63.9)	35 (36.1)	0.0609
Female	30 (47.6)	33 (52.4)	
Total	92 (100)	68 (100)	

FR: Frequent relapse, IFR: Infrequent relapser, SD: Standard deviation

seen between the duration of interval between remission and first relapse for the children with FR (4.74±2.6 months) and with IFR (9.39±2.09 months) (Table 3). In 6.5% children with IFR, history of infections (urinary tract and respiratory tract) was present in comparison to 66.2% children with FR (p=0.0001) (Table 3). Incidence of hypertension was significantly higher (p=0.0001) in children with FR (80.9%) than in children with IFR (5.4%) as shown in Table 3.

However, serum albumin, 24 h urine protein, and azotemia values were not associated with increased risk of the FR in our study. The serum albumin values of the children with FR (2.27±0.34) did not differ significantly from that of the IFR children (2.32±0.34 mg/dl) (p=0.3743). Similarly, 24 h urine proteins of FR (1188.5±562.2) and IFR (1234.3±607) children showed no significant difference (p=0.7647). Majority of the children in both the groups had normal renal function tests.

DISCUSSION

NS generally tends to follow a benign and chronic relapsing course, but a few patients may have serious or fatal complications.

Table 3: Factors significantly correlated with FR (n=160)

Factors	Number of patients (%)		p value
	IFR	FR	
Time taken to achieve remission during first episode (weeks)			
1	72 (78.3)	7 (10.3)	0.0001
2	18 (19.6)	5 (7.4)	
3	2 (2.2)	44 (64.7)	
4	-	12 (17.6)	
Mean±SD	1.24±0.48	2.9±0.81	
Duration of interval between remission and first relapse (months)			
0-1	5 (5.4)	4 (5.8)	0.0001
1-6	4 (4.3)	48 (70.5)	
>6	83 (90.2)	16 (23.5)	
Mean±SD	9.39±2.09	4.74±2.6	
Infections (urinary tract and respiratory infections)			
Present	6 (6.5)	45 (66.2)	0.0001
Absent	86 (93.5)	23 (33.8)	
Hypertension			
Present	5 (5.4)	55 (80.9)	0.0001
Absent	87 (94.6)	13 (19.1)	

FR: Frequent relapse, IFR: Infrequent relapser, SD: Standard deviation

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,* cushingoid 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]. In our study, IFR (57.5%) in children was more common compared to FR (42.5%). Similar findings were reported by Prasun et al. [9] and Noer et al. [18]. However, in several studies, FR was more common than the IFR [5,10,11].

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 is no significant correlation between sex and FR [5,6,10,1617].

Ali et al. [10] and Noer et al. [18] found hematuria as a significant risk factor for the FR. This finding was not supported by Cho et al. [19]; although the presence or absence of hematuria was not determined in our study. In our study, there was no relationship between relapse and serum albumin levels which is supported by the findings of a study by Anderson et al. [15]. However, Sarker et al. showed that the low serum albumin and low serum total protein were related with FR [16]. Azotemia was not significantly related to FR in our study, similar to the study by Ali et al. [10].

The mean time taken to achieve remission was significantly associated with FR in our study. This finding was supported by many other studies [9,10,19-21]. Hence, while we are treating NS children, time taken to achieve remission should be properly noted. Mean duration of interval between remission and first relapse was significantly associated with FR in our study which is also reported in other studies [6,18]. Relapses were triggered by urinary tract infections and respiratory tract infections significantly in our study as reported by Sarker et al. [16], Noer et al. [18], and Misra et al. [22]. Hypertension is another factor significantly associated with FR in our study as similar to the study by Prasun et al. [9].

For IFR, prednisolone (2 mg/kg/day) is given until urine dipstick shows nil or trace for three consecutive days and then prednisolone 1.5 mg/kg on alternate days for 4 weeks. In FR/steroid dependent children, they were referred for evaluation for alternate day prednisolone to maintain remission and to assess steroid threshold. In FRNS and SDNS, the choices include extended low dose (0.5-0.75 mg/kg) alternate day steroids for 6-18 months. In the case of steroid toxicity and threshold >0.5 mg/kg on alternate days, alternate medications such as levamisole, cyclophosphamide, mycophenolate mofetil, tacrolimus, and cyclosporine may be considered. In steroid resistance patients, the child referred for renal biopsy as therapy was based on the renal biopsy findings.

Anderson et al. [15] found a significant relationship between prolonged steroid therapy (>12 weeks) and reduction in relapse frequency in their study. For the treatment of an initial episode of NS, alternate day steroid therapy to be given from 8 weeks to 5 months with tapering of the dose [2]. When planning the duration of steroid therapy, the side effects of prolonged corticoid steroid administration must be kept in mind. In future, stopping steroid therapy as a factor affecting relapse should be studied whether abrupt stopping of steroids after 6 weeks or prolonged duration of steroids with tapering of the dose is helpful to decrease the relapse. If we give importance to factors which are associated with FR in NS, it would be helpful for follow-up and long-term management of the children with NS. It will be helpful to counsel the parents of children with NS, for better drug compliance and for starting alternative drugs, to develop better treatment protocols in future.

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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