Original Article

# Spontaneous remission in nephrotic syndrome relapses followed up for 6 months – A prospective cohort study

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## ABSTRACT

**Background/Objectives:** Nephrotic syndrome (NS) relapses are usually triggered by infections. Treatment of infections will be sufficient to cause resolution of symptoms. Our study aimed to determine frequency of spontaneous remission and its predictors. In addition, our main objective was to know the outcome of children after spontaneous remission of relapses for next 6 months. **Materials and Methods:** Prospective cohort study included all children who presented with NS relapses. Seventy-four children were enrolled from November 2016 to May 2018. Both, spontaneous remission YES and NO groups, were followed up for 6 month duration to study relapse free period and relapse rate. **Results:** About 53.7% relapses remitted spontaneously with only stress dose steroids. Duration of illness more than 24 months could predict likely chances of spontaneous remission RR 0.49, 95% CI 0.29–0.87 (p=0.003). Outcome parameters, that is, relapse free period and relapse rate were similar in both groups. **Conclusion:** About 50% of NS relapses will remit spontaneously with only stress dose of steroids and if required antibiotics. Waiting period of 1 week for clearance of infection and occurrence of spontaneous remission may be necessary before contemplating long steroid course for all relapses. Further studies are required with large sample size.

**Key words:** Nephrotic syndrome, Relapse, Spontaneous remission, Stress dose

Nephrotic syndrome (NS) refers to the tetrad of edema, "nephrotic-range" proteinuria, hypoalbuminemia, and hyperlipidemia. The international study of kidney disease in children (ISKDC) noted in a report that the vast majority of pre-adolescent children with idiopathic NS had minimal change nephropathy on renal biopsy. This histological subtype is the most common cause of NS in children [1].

In developed countries, its incidence is reported to be 20–40 per million population, whereas in Indian subcontinent, it is estimated at 90–100 per million population [2].

Approximately 80% of children achieve complete remission with 4 weeks of corticosteroid therapy after their first presentation and are considered to have steroid-sensitive NS [3,4]. Among children who relapse, about 50% will relapse frequently (defined by the ISKDC as >2 relapses within 6 months of initial response, or >4 relapses in any 12-month period) [5] or will have a steroid-dependent course (defined by Arbetsgemeinschaft für Pädiatrische Nephrologie as >2 consecutive relapses either during corticosteroid therapy or within 2 weeks of ceasing it) [6].

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Despite relapses, most children continue to be steroid responsive, maintain normal kidney function, and, ultimately, will be cured as they age into adolescence and early adult life [4].

It is currently recognized that at least 50% of relapses are triggered by a viral upper respiratory tract infection [5] which may be linked to non-specific host response to infection (cytokine release) rather than to viral antigen or antibody response [7]. Other infections such as urinary tract infection (UTI), diarrhea, peritonitis, and skin infections have also been implicated in triggering the disease [5].

Long-term corticosteroids cause several adverse effects such as short stature, osteoporosis, obesity, cataracts, hypertension and psychological impact. Additionally, they cause endothelial dysfunction in children which can lead to atherosclerosis in adulthood [8]. Treatment with repeated dose of steroids increases the incidence of side effects.

Nevertheless, a significant amount of children go for remission once the infection gets cleared by use antibiotics for 5–7 days. Stress dose of steroids is given [9] to prevent suppression of HPA axis during infections and may not require usual dose of steroids for 5–6 weeks. Taking into view the adverse effect of corticosteroids and very few studies regarding course of spontaneous remission, there is a strong need to conduct the prospective study.

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## MATERIALS AND METHODS

All patients who attended outpatient department and got admitted in the department of pediatrics for NS relapses were evaluated for data. This study is a Prospective cohort study conducted from November 2016 to May 2018. Patients aged 1–18 years old with steroid sensitive NS, children diagnosed to have NS who presents with relapse triggered by infections and children who are not on steroids or on low-dose steroids were included in the study. Children who are on immunosuppressants other than steroids, have secondary NS, and have NS associated with tubercular infections were excluded from the study.

### Methodology

All the patients with NS presenting with relapse triggered by infections were enrolled after taking approval for informed consent. Relapses were managed with treatment of infections symptomatically or with antibiotics if required along with stress dose of steroids (0.5 mg/kg) for 1 week or subsidence of infection whichever earliest. Stress dose of steroids were added to those patients who had taken steroid therapy in past 6 months of dose 2 mg/kg/day for more than 2 weeks.

At start of study, details such as age of patient, sex, age at onset of NS, treatment of first episode, previous relapses, and period of remission before enrolling into our study were taken. Patients were examined for triggering infections – lower respiratory tract infection, spontaneous bacterial peritonitis (SBP), cellulitis, UTI, and chronic suppurative otitis media were classified as "serious" infections and rest other like upper respiratory tract infection (URTI), otitis externa, pyoderma, and dental caries were classified as "benign" infections.

Those who underwent spontaneous remission were categorized into spontaneous remission "YES" group and asked to follow-up every fortnightly until 1 month and then at 2, 4, and 6 months or when they have relapse. Those who did not remit spontaneously within 1 week, were categorized into spontaneous remission "NO" group, and treated according to standard guidelines, that is, 2 mg/kg until remission followed by 4 weeks of alternate day 1.5 mg/kg (Standard Guidelines IAP). These patients were also followed up every fortnightly until 1 month and then at 2, 4, and 6 months or when they have relapse.

During follow-up visits of patients, history and clinical examinations were made to look for any infections or the presence of relapse of NS. Investigations were done if required such as urine routine and complete blood count.

Based on these details, the study outcome was determined – primary objective of our study. Number of relapses occurred in spontaneous remission NO and YES group were counted in 6 month study and extrapolated to get relapse rate (per year). Furthermore, relapse free period was calculated from time of spontaneous remission in YES group/completed steroids in NO group to time taken for first relapse during 6 month study. Mean of relapse free period and relapse rate in each group was compared. Secondary objectives of our study – frequency of spontaneous remission were also calculated. Predictors of spontaneous remission were determined by calculating association between spontaneous remission and each of these parameters such as age, age at onset, duration of illness, duration of remission, sex, and type of infection.

## RESULTS

Among 74 children, most of them, 27 belonged to age group of 7–12 years accounting for 36.5% followed by, 26 belonged to age group of 4–6 years. Least number of children, six belonged to age group of 13–18 years, contributing only 8.1%. There was male preponderance accounting for 72% of study population and rest 28% were female. Hence, male-to-female ratio was 2.6:1. Most number of children had their initial episode of NS in age group of 1–3 years, that is, 40 out of 74. Most number of children, that is, 67.6% relapsed due to URTI, followed by SBP and UTI each contributing 8% each (Fig. 1).

Thirty-nine out of 74 children had spontaneous remission with stress dose steroids or if required antibiotics, accounting for 52.7%. Rest 35 out of 74, that is, 47.3% did not remit spontaneously and required standard treatment of steroids for 2+4 weeks (Table 1).

For predictors of spontaneous remission, only duration of illness >24 months was significant (Table 2). Odds ratio 0.23, 95% CI 0.09 to 0.62 (p=0.003) and RR 0.49, 95% CI 0.29 to 0.87 (p=0.003).

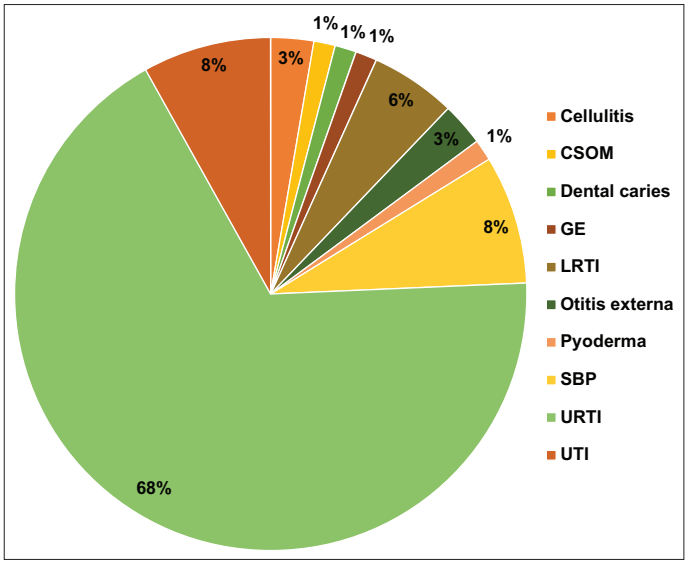


**Figure 1: Pie chart depicting type of triggering infections among study population**

**Table 1: Baseline characters in both the groups**

| Parameters (all in months) | Spontaneous remission YES n=39 | Spontaneous remission NO n=35 |
|---|---|---|
| Age | 85.03 (38.29) | 71.26 (47.39) |
| Age at onset | 46.77 (27.19) | 49.34 (39.02) |
| Duration of illness | 38.26 (30.05) | 21.91 (21.75) |
| Duration of remission | 11.28 (11.82) | 6.89 (7.14) |

**(Mean given in parenthesis)**

Mean relapse free period was 4.46 months in spontaneous remission "YES" group, while, in spontaneous remission "NO" group, it was 4.43 months. Similarly, relapse rate in both groups were 0.56 and 0.66, respectively, not significant statistically.

## DISCUSSION

Our study determined, among 74 children 52.7% underwent spontaneous remission, while 47.3% did not remit spontaneously. Polanco *et al*. [10] did prospective study in 328 children, in cases of idiopathic membranous nephropathy found out spontaneous remission rate to be 32%. Wingen *et al*. [11] conducted study in 32 children, and published spontaneous remission in 23% frequently relapsing NS (FRNS) and 10% of steroid dependent NS (SDNS) cases. Frequency of spontaneous remission was higher in our study as compared to other studies. However, no previous studies have been conducted on infrequently relapsing NS, but literature definitely supports the fact that infection control is sufficient to permit remission in NS.

### Outcome after Spontaneous Remission

From our study results, we could infer that, there would not be any adverse impact in those children who remitted spontaneously and, hence, were not subjected to extra steroids of 2 + 4 weeks. In similar terms, children who did not remit spontaneously and, thus, received standard regimen of relapse treatment, did not had any beneficial effects in terms of prognosis when compared to spontaneously remitted group.

Narchi [12] from Sandwell General Hospital, UK did a short-term prospective study on NS relapses. The standard definition of relapse was significant proteinuria (3+ or 4+) for 3 consecutive days – referred to as P3D on the sulfosalicylic acid test (Fig. 2). He observed 24 consecutive episodes of asymptomatic P3D, without clinical edema occurring due to viral infections in four children (two boys and two girls, age range 2–5 years). In eight of these episodes, serum albumin remained >3 g/dL and proteinuria resolved spontaneously between 5 and 10 days. Sixteen other episodes that happened in three children were regarded as genuine relapses. Later, they had frequent relapses and required cyclophosphamide for one child and levamisole for two children. This observational study challenged the current definition of relapse by the sole presence of protein 3+ on the dipstick. A recommended waiting period of at least 5–10 days before starting therapy was suggested by this study, thus reducing unnecessary treatment of 15–55% of affected children, overdiagnosing frequent relapses, performing a renal biopsy and prolonged steroid courses, and potential side effects of immunosuppressants.

Predictors of spontaneous remission – after thorough search of literature, we could not find any prospective nor retrospective studies pertaining to predictors of spontaneous remission. Age at registration was categorized into two groups – preadolescents 1–9 years and adolescents 10–18 years. These groups compared against study groups, that is, spontaneous remission NO and YES groups. Results were skewed with 83.8%, almost equal contribution from No and YES groups being preadolescents.

**Table 2: Cross-tabulation between duration of illness >24 and spontaneous remission**

| Parameters | Spontaneous remission YES n=39 | Spontaneous remission NO n=35 | Total |
|---|---|---|---|
| Duration of illness >24 months | 11 | 22 | 33 |
| Duration of illness <24 months | 28 | 13 | 41 |
| Total | 39 | 35 | 74 |

**(p=0.003)**

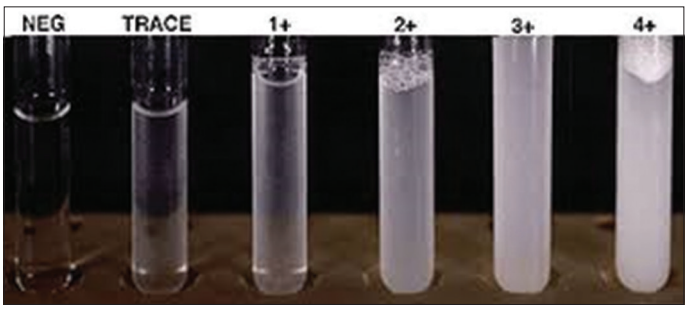


**Figure 2: Sulfosalicylic acid test**

Age at onset of NS was categorized into preschool group 1–6 years and school group 7–18 years. Again results were one sided with equal contribution among study groups, majority 87.8% children found out to have initial presentation in preschool age group.

Similarly, duration of remission categorized into <6 months and more than 6 months, type of infection categorized into benign and serious, and gender did not have statistically significant association with study groups on Chi-square or Fischer exact test.

However, duration of illness categorized into <24 months and more than 24 months had statistically significant association among study groups with $p<0.05$ on Chi-square test. Hence, we could make our prediction if duration of illness was more than 24 months that there would be higher chances of patients undergoing spontaneous remission.

Our study had a few limitations – the follow-up period was short. We cannot comment on the long-term consequences of spontaneous remission. Our study excluded FRNS and SDNS cases, so we could not understand these patients' natural course of relapses. Finally, steroid adverse effects were not studied in our research.

## CONCLUSION

About 50% of NS relapses remitted spontaneously with only stress dose of steroids and if required antibiotics. Duration of illness of more than 24 months was associated with more chances of spontaneous remission. Both study groups', that is, spontaneous remission YES and NO had similar outcome in terms of relapse free period and relapse rate. Treatment of each relapse with standard regimen may not be necessary all the time. Waiting period of 1 week for clearance of infection and occurrence of spontaneous remission is necessary before contemplating long steroid course for all relapses.

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