# A STUDY ON THE CHARACTERISTICS DETERMINING RESPONSE TO STEROIDS AND RELAPSES IN NEPHROTIC SYNDROME IN PAEDIATRIC PATIENTS

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**ABSTRACT**

**BACKGROUND**

Nephrotic Syndrome is a common childhood disease with a high morbidity due to relapses. If there was a way to identify the children who are more likely to relapse, this would give accurate prognosis and facilitate early intervention. The present study observes the characteristics determining response to steroids in nephrotic syndrome and studies whether these characteristics are predictive of subsequent outcome. Thus, targeted interventions may be done based on these identified triggers. This will help to reduce relapses and decrease disease morbidity.

**MATERIALS AND METHODS**

This is a descriptive study done over a period of eighteen months in the paediatric age group (less than 12 years). After enrolment of 55 children with nephrotic syndrome, clinical examination and investigations were done. They were treated and followed up for 1 year. The characteristics of initial presentation were compared with the frequency of relapse.

**RESULTS**

A total of 96.4% of children with nephrotic syndrome responded to corticosteroid therapy. Among 71.9% who relapsed, half had frequently relapsing nephrotic syndrome (FRNS). Among children who took more than 7 days for remission, 64% had FRNS or Steroid dependant nephrotic syndrome (SDNS). In children who had remission within 7 days or less, only 14.3% had FR/SDNS and this was statistically significant. Among the children who had their first relapse in less than 6 months after remission, 84.6% had FR/SDNS. However, only 37.5% of the children who had their first relapse after 6 months following remission had FR/SDNS, and this was statistically significant.

**CONCLUSION**

The risk of a child developing frequent relapses and steroid dependence are increased with shorter time to first relapse and longer time for remission in the initial episode.

**KEYWORDS**

Nephrotic Syndrome, Relapse, Corticosteroid, Infection.

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## BACKGROUND

Nephrotic syndrome is diagnosed by oedema and hyperlipidaemia (cholesterol >200 mg/dL), all arising from large urinary losses of protein. It affects 1-3 per 100,000 children of less than 16 years of age. Childhood nephrotic syndromes are most commonly caused by one of two idiopathic diseases: minimal-change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). A third distinct type, membranous nephropathy, is rare in children. Corticosteroids are the mainstay of therapy for MCNS of which 80-90% of children respond to therapy.

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Relapse of nephrotic syndrome is defined as a urine protein: creatinine ratio of >2 or ≥3+ protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections.[1] While most children with nephrotic syndrome respond to corticosteroids, 80% experience a relapsing course.[2] The chief complications of nephrotic syndrome are infection, thromboembolic events, hypertension, hyperlipidaemia, features of corticosteroid toxicity and behavioural disorders.[3] The risks of a child developing frequent relapses or becoming steroid-dependent are increased with the number of relapses in the first 6 months after initial treatment, younger age at the initial episode, in boys, prolonged time to first remission, haematuria in first episode, shorter time to first relapse and infection at first relapse.[4-9] The most consistent indicator for a frequently relapsing course is early relapse after initial treatment. Studies have not assessed whether the other factors are independent risk factors for predicting frequent relapses or steroid dependence.[10]

The present study provides data about the characteristics determining response to steroids in Nephrotic syndrome. It attempts to identify predictive factors, by studying whether these characteristics of initial response to steroids and course during early phase of disease are predictive of subsequent outcome. Thus, it is hoped that targeted interventions based on identified triggers will reduce relapses and decrease disease morbidity.

## MATERIALS AND METHODS

This was a prospective hospital-based study conducted in Jubilee Mission Medical College & Research Institute, Thrissur in children less than twelve years during an eighteen-month period from 1-1-2016 to 30-6-2017. The minimum required sample size was calculated as 51. Considering the possibility of dropouts, 55 consecutive children with Nephrotic syndrome admitted in the department of paediatrics were recruited for the study.

All willing patients during the study period, below 12 years, admitted in the paediatric department with diagnosis of initial episode and relapse of nephrotic syndrome were included in the study. Patients aged more than 12 years and patients who did not give consent for the study were excluded from the study.

A detailed physical examination was done. Investigations done were complete blood count, ESR, blood urea, serum creatinine, serum cholesterol and serum albumin. Urine samples were examined for the presence of gross haematuria or cloudy appearance followed by microscopic examination to look for pus cells, RBC, casts and urine culture. Other relevant investigations were done and entered in the proforma for all patients to look for associated complications. Blood pressure, weight, intake and output chart, abdominal girth and urine for proteinuria were daily recorded for all patients. Oral prednisolone was administered as a single daily dose starting at 60 mg/m$^2$/d or 2 mg/kg/day for 4–6 weeks followed by alternate-day medication as single daily dose starting at 40 mg/m$^2$ or 1.5 mg/kg (maximum 40 mg on alternate days) and continued for 2–5 months with tapering of the dose. Infrequent relapses in children were treated with a single-daily dose of prednisolone 60 mg/m$^2$ or 2 mg/kg (maximum of 60 mg/d) until the urine albumen became 'nil' for three consecutive days when the child achieved remission. After achieving complete remission children were given prednisolone as a single dose on alternate days (40 mg/m$^2$ per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. Relapses in children with frequent relapses or steroid dependent nephrotic syndrome were treated with daily prednisolone until the child achieved remission, followed by alternate-day prednisone for at least 3 months. Daily prednisolone at the lowest dose was given to maintain remission without major adverse effects in children with steroid dependence, where alternate-day prednisone therapy was not effective. Daily prednisone was given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with frequent relapse and steroid dependent nephrotic syndrome already on alternate-day prednisolone. Response of patients treated with steroids was noted and followed up for a duration of one year. The outcome of steroid therapy was categorized as according to KDIGO (2012) guideline[10] definitions for nephrotic syndromes according to number and frequency of relapse and response to steroid therapy. We then compared the characteristics in the initial presentation with frequency of subsequent relapse of patient. The initial characteristics included in the comparison were age, sex, hypertension before starting steroid therapy, gross haematuria, serum albumin, serum cholesterol, time taken for remission after starting steroid therapy in initial episode and time from remission to first relapse. The outcome was measured as two groups: patients with no relapse and infrequent relapsers taken as one group, and frequent relapsers and steroid dependent patients as another.

### *Statistical Methods and Data Analysis*

To test for statistical significance of associations based on percentages, Chi-square tests were used. Fisher's exact was used for two by two tables when the expected count is less than 5. For data entry Microsoft excel was used and statistical analysis was done using IBM SPSS Statistics for Windows version 21.0. 23.

## RESULTS

A total of 55 children were recruited for the study, of which only two children did not respond to steroids, the rest of the children had complete remission (Table 1). Among the ones who responded, 16 had no further relapses during the period of the study, 24 had relapses only after 6 months and 13 had relapses within 6 months of remission (Table 2). There were 4 steroid dependent children. Among the ones who relapsed, 17 had infrequent relapses, and 16 had frequent relapses. (Table 3)

FR/SDNS was more in children in the age group of 2-6 years (43.6%) against 21.4% in the 7-12 years age group, but this was not statistically significant (p value-0.142) (Table 4). It was noted that FR/SDNS was more common in boys (45.2%) than in girls (27.3%), but this was not statistically significant (p value-0.186). Children who presented with haematuria had more frequent relapse (75%) but this was not statistically significant (p-0.145). Children who presented with hypertension before starting steroid therapy had more frequent relapse (50%) but it was not significant (p-0.457). Children with serum albumin <1.5 g/dl had more FR/SDNS, but it was not significant on statistical analysis with p value of 0.071. Children with serum cholesterol >400 mg/dl had more FR/SDNS, but this was not statistically significant with p value 0.591. In children who took more than 7 days for remission after starting treatment, 64% had FR/SDNS, but in children who had remission within 7 days or less, only 14.3% had FR/SDN. This was statistically significant with a p-value of <0.001. In children who had their first relapse in less than 6 months after remission, 84.6% had FR/SDNS. However, the frequency of FR/SDNS was only 37.5% in the children who had their first relapse after 6 months following remission. This was statistically significant with a p-value of 0.006.

| Treatment Response | Number of Patients | Percent |
|---|---|---|
| Complete remission | 53 | 96.4 |
| No remission | 2 | 3.6 |
| **Total** | **55** | **100.0** |

***Table 1. Treatment Response***

| Time from Diagnosis to First Relapse | Number of Patients | Percent |
|---|---|---|
| No relapse | 16 | 29.1 |
| >6 months | 24 | 43.7 |
| <6 months | 13 | 23.6 |
| SRNS | 2 | 3.6 |
| **Total** | **55** | **100.0** |

***Table 2. Time from Diagnosis to First Relapse***

| Classification | Number of Patients | Percent |
|---|---|---|
| No relapse | 16 | 29.1 |
| Infrequent relapse | 17 | 30.9 |
| Frequent relapse | 16 | 29.1 |
| Steroid dependent | 4 | 7.3 |
| Steroid resistant | 2 | 3.6 |
| **Total** | **55** | **100.0** |

***Table 3. Classification of Outcome after Steroid Therapy***

| | | Outcome | |
|---|---|---|---|
| | | **Nil/ Infrequent Relapse** | **Frequent Relapse/ Steroid Dependence** |
| Age | 2-6 years (39) | 56.4% (22) | 43.6% (17) |
| | 7-12 years (14) | 78.6% (11) | 21.4% (3) |
| Sex | Male (31) | 54.8% (17) | 45.2% (14) |
| | Female (22) | 72.7% (16) | 27.3% (6) |
| Haematuria | Yes (4) | 25% (1) | 75% (3) |
| | No (49) | 65.3% (32) | 34.7% (17) |
| Hypertension | Yes (8) | 50% (4) | 50% (4) |
| | No (45) | 64.4% (29) | 35.6% (16) |
| S. Albumin | <1.5 g/dl (26) | 50% (13) | 50% (13) |
| | ≥1.5 g/dl (27) | 74.1% (20) | 25.9% (7) |
| S. Cholesterol | <400 mg/dl (24) | 58.3% (14) | 41.7% (10) |
| | ≥400 mg/dl (29) | 65.5% (19) | 34.5% (10) |
| Time for remission in first episode | ≤7 days (28) | 85.7% (24) | 14.3% (4) |
| | >7 days (25) | 36% (9) | 64% (16) |
| Time from remission to first relapse | >6 months (24) | 62.5% (15) | 37.5% (9) |
| | <6 months (13) | 15.4% (2) | 84.6% (11) |

***Table 4. Prediction of Outcome from Initial Characteristics***

## DISCUSSION

Nephrotic syndrome is a common clinical disease in childhood, responsible for a high degree of morbidity. The morbidity is predominantly due to the relapses that can occur through-out childhood. The purpose of the study was to identify the characteristics that determine response to steroids in Nephrotic Syndrome and to determine if there was a relationship between these characteristics and the frequency of future relapses.

FR/SDNS was found to be more in children in the age group of 2-6 years (43.6%) when compared to the 7-12 years age group (21.4%), but this was not statistically significant (p value-0.142). It was noted that FR/SDNS was more common in boys (45.2%) than in girls (27.3%), but this was not statistically significant (p value-0.186). Lewis et al and Andersen et al observed that frequent relapses were more common with young age of onset and in boys.[5,6]

Children who presented with haematuria had more frequent relapses (3 out of 4) but this was not statistically significant (p -0.145). Children who presented with hypertension before starting steroid therapy also had more frequent relapses (4 out of 8) but this was not significant (p-0.457).

On comparing the laboratory data, children with serum albumin <1.5 g/dl and serum cholesterol >400 mg/dl had more FR/SDNS but neither was significant on statistical analysis with p value of 0.071 and 0.591 respectively. Jahan et al demonstrated that low serum albumin level at the time of initial attack as an independent risk factor for frequent relapse and that this can be used as a predictor of FRNS.[11]

In children who took more than 7 days for remission after starting treatment, 64% had FR/SDNS, but in children who had remission within 7 days or less, only 14.3% had FR/SDNS and this was statistically significant with a p-value of <0.001. In children who had their first relapse in less than 6 months after remission, 84.6% had FR/SDNS. Only 37.5% of children who had their first relapse after 6 months following remission had FR/SDNS and this was statistically significant with a p-value of 0.006. A recent study done by Noer concluded that the statistically significant predictors of relapse were the time-interval between early steroid response and the first relapse, number of relapses within the first 6 months, infection during the first relapse, haematuria and sex.[9] In the present study a statistically significant relation was found between the frequency of relapse and time taken for remission in the first episode and time taken for first relapse. FR/SDNS is more common in children who took more time for remission in the initial episode and those who had first relapse earlier. Thus, these characteristics were statistically significant predictors for frequent relapse.

## CONCLUSION

The risk of a child developing frequent relapses or becoming steroid-dependent is significantly increased with shorter time to first relapse and longer time for remission and these may be noted to predict subsequent relapse. This data will help in the early identification of children with frequent relapses and thus enable better care. Targeted interventions based on identified triggers will reduce relapses and disease morbidity. This study emphasizes the need for larger multicentric trials to define predictors for relapse in nephrotic syndrome.

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