Analysis of Predictors of Relapse in Children with Steroid Sensitive Nephrotic Syndrome

Bhatta M[1], Shah GS[2], Mishra OP[3]

Abstract

Introduction: Children with idiopathic nephrotic syndrome (INS) are steroid responsive but have relapses in subsequent non-treatment period. The objective of the present study was to analyze the factors which could predict relapses in these children. **Material and Methods:** Forty patients of INS aged 1-14 years of both gender were enrolled over one year period and followed for six months after treatment of initial episode of Nephrotic Syndrome. **Results:** The median age of children was 4.5 years and male to female ratio 1.9:1. There were 24(60%) relapses and 16(40%) non-relapses. The relapses had significantly higher mean total leukocyte count, serum urea, potassium and cholesterol than non-relapses. It was also observed that the median age of onset in relapses was significantly lower than non-relapses ($p<0.001$). Also, the median time to response to steroid therapy was longer in relapses than non-relapses ($p<0.001$). Children who relapsed had infections at the time of relapse. **Conclusion:** Thus, onset of disease in younger age group, late response to steroid therapy and presence of infections were found to be associated with relapses in these children.

Key words: Nephrotic syndrome, Factors, Relapses.

Introduction

The annual incidence of idiopathic nephrotic syndrome (INS) in children is 2-7 /100,000 populations below 1-16 years of age[1]. The patients are usually treated with oral prednisolone as per APN protocol (prednisolone 60 mg/m^2/day for 6 weeks, followed by 40 mg/m^2/every alternate days for 6 weeks)[4]. However, about 70% of the children experience relapsing course in the next 12 months non-treatment period[3]. The relapses are often precipitated by infections[6,9,14] which become troublesome for the patients as well as parents. Certain factors such as age, gender, time to response, duration of treatment of initial episode and frequency of relapses in the initial six months have been found to predict the relapses in these patients[1,10,16]. However, there has been inconsistency in the literature and also paucity of reports from our country to determine precisely that which factors are really responsible for, and reliably predict the relapses.

The objectives of this study were to analyse different factors causing relapses in children with INS.

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Material and Methods

This was a prospective descriptive hospital based study conducted during the period of April 2014 to March 2015. All the children, aged 1-14 years, who attended the pediatric nephrology clinic with diagnosis of first episode of INS presenting with generalized edema, hypoalbuminemia (serum albumin, <2.5mg/dl), heavy proteinuria (urine protein/creatinine >2 mg/mg) and hypercholesterolemia (serum cholesterol >200mg/dl) were enrolled in the study. The exclusion criteria were those children who had received prednisolone or any other immunosuppressive drugs in the preceding two weeks, had systemic diseases known to cause nephrotic syndrome, received incomplete duration of steroid treatment, and parents not willing to participate in the study, A total of forty patients satisfied the inclusion criteria and were enrolled. The study protocol was approved by the Institutional Ethical Review Board of the institute.

The detailed demographic profile such as age, gender, weight, duration of illness and general physical and systemic examination findings were recorded in a standard predesigned proforma. The investigations included haemogram, serum albumin, cholesterol, urea, creatinine, sodium, potassium, HBsAg and HIV screening, urine gross and microscopic examination, urine protein/ creatinine ratio and urine culture sensitivity. The X-ray chest, ultrasound of kidneys, ureter and bladder, Monteux test, ASO titer, serum C3, C4, ANA, anti Ds DNA were done, whenever indicated.

Treatment and follow up: All cases of first episode of nephrotic syndrome were given prednisolone as per APN guideline i.e. Prednisolone (60mg/m^2/day in 2–3 divided doses for 6 weeks, followed by 40 mg/ m^2 in a single morning dose given on alternate days for 6 weeks)[4]. The patients were followed after start of treatment to observe time of remission using dipstick test. The children having infections like respiratory Tract Infections, urinary Tract Infections, diarrhea and fever without focus were treated as per hospital protocol.

Thereafter, all patients were followed for next 6 months in the paediatric nephrology clinic for occurrence of infections, frequency of relapses and any other illness. Patients were categorized during follow-up into remission (urine protein/creatinine of <0.2 mg/mg or urine albumin nil or traces for three consecutive early morning specimens), relapse (urine protein/creatinine of >2mg/mg or urine albumin 3+(plus) or more by dipstick test for three consecutive days, having previously been in remission), infrequent relapses (less than two relapses within six months) and frequent relapses (two or more relapses within six months) depending on their response to therapy. Accordingly, infrequent relapses were treated with prednisone, 60 mg/m^2/day, until remission, followed by 40 mg/ m^2 single morning dose on alternate days for 4 weeks. In patients with frequent relapses, prednisolone was tapered gradually over 12–18 months to a minimum of 0.25–0.5 mg/kg after achieving remission with 2 mg/ kg/day.

Statistical analysis: The data was analyzed using SPSS version 21 software. Student's t- test was used for comparison of data showing normal distribution, Man-Whitney U test for non-Gaussian distribution and Chi-square test for categorical variables between relapses and non-relapses. A *p* value of <0.05 was considered significant.

Results

Of the 40 patients with INS, there were 18 males (64.3%) and 10 females (35.7%) in the age group of 1-6 years, while the corresponding figures were 8 (66.7%) and 4 (33.3%), respectively in 7-14 years. Overall the median age of onset was 4.5 years and male to female ratio was 1.9:1. Twenty six cases (65%) were from rural while 14 (35%) were from urban area. There were four patients (10%), who had hypertension (defined as blood pressure >95th percentile for height, age and gender on three or more occasions), haematuria (defined as ≥5 red blood cells/high-power field) and azotaemia (defined as rise of serum creatinine level of >50% from the baseline with regard to age and gender; upper limit of normal, 0.9 mg/ dl in male and 0.7 mg/dl in female patients ±0.2 mg/dl for each); all of them were above 6 years. Anaemia (defined as hemoglobin <11 g/dl in 1–6-year-old and <12 g/dl in 7–13-year-old patients) was seen in 6 (15%) patients. Thirty patients (75%) were of normal nutritional status, (weight calculated after disappearance of oedema), 6 (15%) were undernourished and 4 (10%) were obese.

After completion of 12 weeks of prednisolone treatment, the children were regularly followed at 2-4 weeks interval for six months period. There were 24 (60%) relapses and 16 (40%) non-relapses. It was found that relapses had lower median age of onset of disease and took longer time to achieve remission than non-relapses (p<0.001).The mean total leukocyte count, serum urea, potassium and cholesterol had significant differences between the two groups.

The data of age of onset and time to achieve remission in the age group of 1-6 and 7-14 years of age group are depicted in Figure 1 and Figure 2, respectively. It was found that significantly higher proportion of children had relapses who had disease onset between 1-6 years in comparison to 7-14 years of age group (71.4% vs 33.3%; p=0.024). Further, the children who responded between 3-4 weeks of start of prednisolone

treatment had higher percentage of relapses than 1-2 weeks (100% vs 27.3%; *p*<0.001).

All the patients who had relapse had some sort of infections as the triggering factor, and none of the non-relapses had infections. There were 10 cases (25%) of respiratory tract infection, 6 (15%) with urinary tract infection (based on the clinical features, positive pus cells and positive urine culture i.e. growth of single organism of >10^5cfu/ml in a mid-stream urine sample), 4 (10%) with gastrointestinal tract infections and another 4 (10%) cases of fever without focus.

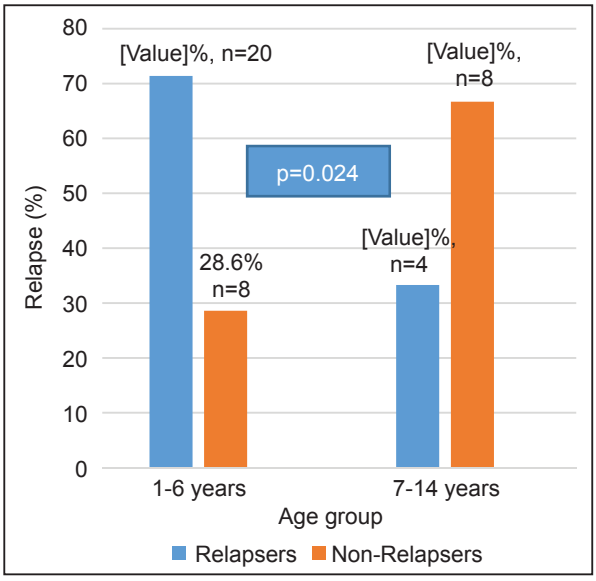

Fig 1: Relationship between ages of disease onset with occurrence of relapse.

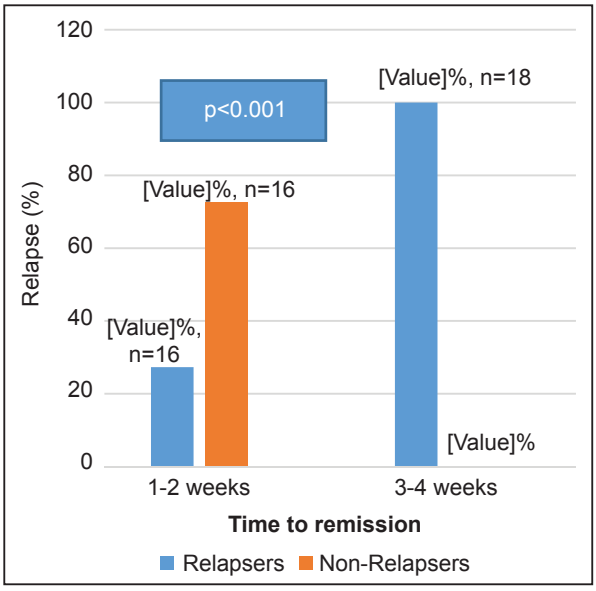

Fig 2: Comparison of time to achieve remission and occurrence of relapses.

Discussion

As such, the children with INS are steroid sensitive. However, relapses are really a troublesome feature in this disease. Overall, male to female ratio in our study was about 2:1 which is similar to findings of others[1,7]. Noer reported that male gender had predilection for relapses but this was not observed in the present series[10]. Further, we did not find any difference between male and female patients as regard to the time of remission; in contrast Suresh kumar et al observed that males achieved remission faster than female counterparts in their study[13]. The median age of onset was 4.5 years and it is because of the fact that this is the peak period for occurrence of steroid responsive nephrotic syndrome in children. Four patients had hypertension, hematuria and azotemia at the time of presentation and they were between 7-14 years of age; similar to the findings of Damanik[2]. In the past Mishra et al found that these features were comparable among all the age groups (1-3, 4-6 and 7-14 years)[7]. However, these odd features had no association with frequency of relapses in our patients; a finding dissimilar to the observation of Noer which showed hematuria as one of the factor for prediction of relapses[10]. Further, Siegel et al reported that hypertension, azotemia and hematuria had a significant correlation with the frequency of relapses in the first 2 years[11].

Sixty percent of the patients had infections at the time of relapse also supported by the presence of significant leucocytosis in relapses. As such occurrence of infections in developing countries is a common phenomenon and it is due to the fact that patients with nephrotic syndrome are immune-compromised. Because of infection, there is expression of interleukin-13 messenger RNA, leading to release of vascular permeability factors from monocytes thus causing proteinuria[18]. Similar phenomenon has been hypothesized by Mishra et al[8]. The proportion of patients experiencing relapses was found to be ranging between 63.6% to 90%[7,10,12]. However, these studies[7,8,10,12] included a longer duration of follow up than our observation.

The age of disease onset had inverse relationship with frequency of relapses in our study, which is similar to the findings of Mishra et al[7] and Kabuki et al[5]. The exact explanation of this finding is unknown. Further, it was also observed that those children who took longer time for remission had higher percentage of relapse. Similar observations have been reported by previous authors[1,7]. Vivarelli et al reported median time to response in non-relapses was shorter than relapses in their series[17].

However, the present study has certain limitations such as smaller number of study subjects and shorter duration of follow-up period. Therefore, these findings can be further confirmed in a larger sample size and longer duration of follow up in a multi-centric study in future.

Conclusion

The age of onset of disease and time of response to steroids emerged as significant predictors of relapse in these cases. Thus, it may be possible to counsel the parents to explain future course of illness in terms of relapses.

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