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Original Research Article

INCIDENCE AND PREDICTORS OF RELAPSE IN CHILDREN WITH FIRST EPISODE OF NEPHROTIC SYNDROME: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Childhood nephrotic syndrome frequently relapses despite good steroid response, and early predictors remain clinically important for follow-up. This study assessed the relapse incidence and predictors in children with first-episode nephrotic syndrome relative to remission timing. **Materials and Methods:** A prospective observational study was conducted in a tertiary care paediatric department over 15 months among children with first-episode nephrotic syndrome. Baseline demographic and clinical data were recorded using a structured pro forma. Laboratory investigations and imaging were performed as previously described. All children received prednisolone according to standard guidelines and were monitored using daily urine protein dipsticks. Patients were treated for intercurrent infections and followed up for six months for remission, relapse, and outcomes. **Result:** Fifty children were studied, with a mean age of 3.24±1.01 years; females were 52% and rural residents 64% were rural residents. Moderate acute malnutrition was observed in 50% of the patients. At diagnosis, UTI occurred in 38%, RTI in 30%, and no infection in 28% of the patients. Hypertension was observed in 30% of patients, haematuria and azotaemia in 10% each, with normal complement levels in all. Remission occurred within 0-8 days in 42%, 9-14 days in 32%, and >14 days in 26%, with relapse rates of 47%, 93%, and 100%, respectively. Overall, 72% had one relapse, and 4% had two. Relapse was higher with male sex, rural residence, infection, hypertension, and delayed remission. **Conclusion:** Relapse after the first episode of nephrotic syndrome is common and strongly associated with delayed remission, hypertension, infection, and male sex. Early risk stratification enables targeted monitoring and the implementation of preventive follow-up strategies.

INTRODUCTION

Childhood nephrotic syndrome is a common paediatric kidney disease characterised by nephrotic-range proteinuria, hypoalbuminaemia, oedema, and hyperlipidaemia, with high hospitalisation rates and serious complications at 16 per 100,000.[1] Features include nephrotic-range proteinuria (≥40 mg/m²/hour), hypoalbuminaemia (<25 g/L), oedema, and hyperlipidaemia, with 71% of patients experiencing hospitalisation at 0.5 hospitalisations per patient-year and serious complications in 14% of patients.[2] Thromboembolism has been reported in 3.60% of cases and up to 8.70% in congenital forms. The risk of infection, including life-threatening pneumococcal infections, is increased. Long-term prognosis depends more on the pattern of proteinuria remission than on the initial histology.[3,4]

Corticosteroids achieve remission in 80% of children with first-episode idiopathic nephrotic syndrome, but 90% of these children experience relapse, with the initial treatment response being a predictor of long-term outcomes. First-episode nephrotic syndrome (FENS) is commonly reported in children aged 1-6 years with proteinuria (mean 148±70 mg/kg/day), hypoalbuminaemia, and hypercholesterolaemia.[5] Standard management involves 12-week corticosteroid courses (prednisolone 2 mg/kg/day). Remission occurred within 15.8±2 days on average, while relapse referred to the recurrence of nephrotic-range proteinuria.[5,6] Early response predicts a lower relapse risk than a delayed response. Initial remission

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during therapy shows a positive prognosis, with an early response defining the disease course.

Childhood nephrotic syndrome has a high relapse risk (71.9%), with relapses classified as infrequent, frequent, or steroid-dependent, requiring early identification of high-risk children to minimise steroid toxicity and morbidity. A meta-analysis of 73 studies found a pooled relapse risk of 71.9% (95% prediction interval: 38.8-95.5%), decreasing from 87.4% to 66.2% between 1945 and 2011.[7] Prospective cohort studies have identified predictors of frequent relapses and a time to the first relapse of <6 months. Prolonged steroid therapy causes side effects, including osteoporosis and excess weight.[8-10] These studies provide limited data on the impact of these conditions on QoL. Early identification enables targeted interventions to reduce relapse-related morbidities.[11]

The time to remission (TTR) predicts relapse in nephrotic syndrome, with delayed remission linked to a higher relapse risk. Situmorang et al. (n=90) found TTR ≤6 months as a strong predictor (OR 37.113, 95% CI 7.115-193.595), and Prasun et al. (n=88) noted remission after 2+ weeks led to frequent relapses.12,13 Other predictors include male sex, younger age, hypoalbuminaemia, and prolonged TTR with severe proteinuria and hyperuricaemia.[12-14] While most children remit with corticosteroids, many relapse, causing hospitalisations and increased steroid exposure. The clinical course varies, making relapse prediction difficult. Demographic, clinical, and laboratory factors are suggested predictors. Most evidence comes from retrospective studies with variable protocols, limiting their clinical use. Prospective studies on first-episode nephrotic syndrome are needed to obtain reliable data on relapse and predictors. Understanding relapse patterns is important for follow-up, monitoring, caregiver counselling, and treatment guidance.

Aim: This study aimed to assess the incidence of relapse and identify predictors among children with first-episode nephrotic syndrome with respect to time to remission.

MATERIALS AND METHODS

This prospective observational study was conducted in 50 children with a first episode of nephrotic syndrome in the Department of Paediatrics, Government Vellore Medical College and Hospital, Tamil Nadu, over a period of 15 months (September 2021 to January 2023). The Institutional Ethics Committee of Government Vellore Medical College and Hospital approved the study. Written informed consent was obtained from parents or guardians, and confidentiality was maintained.

Inclusion Criteria

Children aged 1-12 years who attended the paediatric clinic with a diagnosis of the first episode of nephrotic syndrome presenting with generalised oedema, hypoalbuminaemia (serum albumin, <2.5 mg/dl), heavy proteinuria (urine protein/creatinine >2 mg/mg), and hypercholesterolaemia (serum cholesterol > 200 mg/dl).

Exclusion criteria

Children who had received prednisolone or any other immunosuppressive drugs in the preceding two weeks, with systemic diseases known to cause nephrotic syndrome, received an incomplete duration of steroid treatment, and were not willing to participate in the study.

Methods: Demographic details, including age, sex, weight, illness duration, and examination findings, were recorded in a standard proforma. Investigations included haemogram, serum albumin, cholesterol, urea, creatinine, sodium, potassium, HBsAg, and HIV screening, urine examination, protein/creatinine ratio, and culture sensitivity. Chest X-ray, ultrasound of the kidneys, ureters, and bladder, the Mantoux test, ASO titre, serum C3, C4, ANA, and anti-Ds DNA were performed when indicated. First-episode nephrotic syndrome cases received prednisolone according to the APN guidelines. Patients were monitored for remission using daily dipstick tests for proteinuria after initiating oral prednisolone. Children with infections such as respiratory tract infections (RTI), urinary tract infections (UTI), diarrhoea, and fever were treated according to the hospital protocol. All patients were followed up for 6 months in the paediatric OPD for infections, relapses, and other illnesses. Patients were categorised during follow-up, and the data are presented as frequencies, percentages, means, and standard deviations.

Definition: Remission was defined as a negative/trace urine protein for three consecutive days. Relapse was defined as urine protein ≥2+ for three consecutive days after remission. Delayed remission occurred after eight days of steroid therapy.

Statistical analysis: Data were presented as mean and standard deviation for continuous variables and as frequency and percentage for categorical variables. Continuous variables were compared using the independent sample t-test. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. A p-value < 0.05 was considered statistically significant using a two-tailed test. Data analysis was performed using IBM SPSS Statistics version 25.

RESULTS

The mean age of the children was 3.24 ± 1.01 years (range: 2-5 years). The average body weight was 12.86 ± 2.43 kg (range: 10-20 kg), and the average height was 95.78 ± 7.3 cm (range: 84-112 cm). Female children were predominant (52%), and most children were from rural areas (64%). Moderate acute malnutrition was the most common (50%), followed by well-nourished status (44%), overweight (4%),

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and obesity (2%). The most common associated infections at diagnosis were UTI (38%), RTI (30%), and gastroenteritis (4%), while 28% had no infection at initial presentation [Table 1].

Table 1: Baseline Demographic and Clinical Characteristics of Patients

		N (%)
Age (Mean ± S.D.) (in years) (Range: 2-5 years)		3.24 ± 1.01
Weight (in Kg) (Range: 10-20 Kgs)		12.86 ± 2.43
Height (CM) (Range: 84-112 CMs)		95.78 ± 7.3
Sex	Male	24(48%)
	Female	26(52%)
Residence	Rural	32(64%)
	Urban	18(36%)
Nutritional status	Moderate acute malnutrition	25(50%)
	Well nourished	22(44%)
	Overweight	2(4%)
	Obese	1(2%)
Infection at first diagnosis	UTI	19(38%)
	RTI	15(30%)
	Gastroenteritis	2(4%)
	No infection	14(28%)

Among the children, hypertension was reported in 30%, while 70% did not have hypertension, and haematuria was observed in 10% of patients, while 90% did not show it. Azotaemia was present in 10% of patients and absent in 90%, and all patients showed normal complement levels [Table 2]. Among the study population, the mean cholesterol level was 369.54 ± 94.26, and the mean triglyceride level was 283.04 ± 76.15.

Table 2: Distribution of Clinical and Laboratory Findings Among Patients

		N (%)
Hypertension	Present	15(30%)
	Absent	35(70%)
Haematuria at 1st episode	Present	5(10%)
	Absent	45(90%)
Azotaemia	Present	5(10%)
	Absent	45(90%)
Hypocomplementemia	Present	0
	Absent	50(100%)

The time to remission showed a graded distribution, with 42% achieving remission within 0-8 days, 32% within 9-14 days, and 26% > 14 days. Relapse rates increased with longer remission times, with 47% for 0-8 days, 93% for 9-14 days, and 100% for patients requiring over 14 days to achieve remission [Table 3].

Table 3: Time to Remission and Relapse Status at the Time of Remission Among Patients

		N (%)	Relapse at the time of remission
Time to remission	0–8 days	21(42%)	10(47%)
	9–14 days	16(32%)	15(93%)
	>14 days	13(26%)	13(100%)

Most children experienced a single relapse (72.0%), while 24.0% had no relapse, and 4.0% had two relapses. Regarding infections at relapse, 62.0% of patients reported no infection, and among those with infections, RTIs were more common (22.0%) than UTIs (16.0%) [Table 4].

Table 4: Distribution of Number of Relapses and Associated Infections at Relapse

		N (%)
Number of relapses	No relapse	12(24.0%)
	One relapse	36(72.0%)
	Two relapses	2(4.0%)
Infection at relapse	No infection	31(62.0%)
	RTI	11(22.0%)
	UTI	8(16.0%)

Analysis showed that relapse was more common in male children than in females ($p = 0.013$), and children from rural areas reported higher relapse rates than urban residents ($p = 0.011$). Infection during the first episode was linked to subsequent relapse ($p = 0.003$), and hypertension showed a strong association with relapse ($p = 0.009$). Delayed remission was a strong predictor ($p<0.001$) [Table 5].

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Table 5: Clinical Factors Associated with Higher Risk of Relapse Among Patients

Variable	Observation	P value
Male sex	Higher relapse observed	0.013
Rural residence	Higher relapse observed	0.011
Infection at first episode	Associated with relapse	0.003
Hypertension	All hypertensive children relapsed	0.009
Delayed remission	Strong predictor of relapse	<0.001

DISCUSSION

In our study, first-episode nephrotic syndrome was predominantly observed in young children, with a slight female predominance but higher male relapse rates. Most patients were from rural areas, which was associated with an increased likelihood of relapse. Moderate acute malnutrition accounted for a major proportion of cases, showing that undernutrition remains common. Age findings align with those of Shanta et al., who found that younger age at onset was associated with frequent relapses.[15] These findings suggest that demographic and socioeconomic factors influence disease presentation and relapse.

Gender-related findings vary, with Akter et al. reporting 61.31% male participants and higher male relapse rates (n=168), while Shanta et al. found a 2:1 male: female ratio (n=75).[15,16] Findings on rural residence are mixed. Shanta et al. noted that rural inhabitants were strongly associated with frequent relapses, although this was not significant.[15] Albar et al. identified nutritional status as a significant relapse risk factor (n=142, P<0.05).[17] Minj et al. found that 77.1% of patients with lower socioeconomic status were frequent relapsers (n=80).[18] The findings show that demographic and socioeconomic factors influence nephrotic syndrome patterns, although the evidence strength varies across studies.

Children in our study had associated infections at first presentation, mainly urinary and RTIs. Some patients had hypertension, whereas fewer showed haematuria and azotaemia. Complement levels were normal, and infection during the first episode and hypertension were associated with subsequent relapse. At relapse, most children lacked infection, although some had respiratory infections more than urinary infections. Tariq et al. followed 270 children with SSNS and found that 79.6% (215 patients) relapsed following infection, with upper RTIs (37.8%) and lower RTIs (21.1%) being most frequent.[19] Lora et al. (2021) reported 28% infection rates in newly diagnosed cases (76 children), with ARI and UTI at 34.21% and 26.32%, respectively.[20] Thus, our findings on infection-associated presentations and relapse risk in paediatric nephrotic syndrome are supported by multiple studies, varying by study populations, locations, and diagnostic criteria.

In our study, remission was achieved at different times, with patients in the early and delayed remission groups. A pattern emerged between remission time and relapse, with later remission showing a higher relapse risk. Delayed remission was a strong indicator of future relapse, supporting its use in risk prediction and follow-up planning. Situmorang et al. studied 90 patients, finding remission ≤6 months as a strong risk factor (OR 37.1, 95% CI 7.1-193.6).[12] Prasun et al. found that remission after 2 weeks predicted frequent relapses in 88 cases, while Bajeer et al. confirmed that delayed steroid response predicted earlier first relapse in 57 children.[13,21] Delayed remissions consistently predict relapse in paediatric nephrotic syndrome, with studies showing a dose-response relationship.

Our study identified factors linked to relapse risk: male sex, rural residence, and infection during the first episode. Hypertension at presentation was strongly linked to relapse, with all hypertensive children relapsing. Delayed remission was the strongest predictor of a higher relapse probability. These findings suggest the use of clinical indicators and remission timing to assess the relapse risk in children with first-episode nephrotic syndrome. Akter et al. found that males were 3.04 times more likely to relapse (95% CI=1.09-8.45) and respiratory infection increased relapse odds to 4.43 (95% CI=1.26-15.53).[8] Prasun et al. and J. Balaji et al. (2017) reported a significant association between hypertension and frequent relapses.[13,22] Identifying children with these risk factors requires closer monitoring, infection control, blood pressure management, adherence reinforcement, and relapse prevention counselling. The use of these predictors can optimise surveillance and steroid response monitoring from the first episode.

Limitation

The single-centre design, small sample size, and short follow-up period of this study may limit the generalisability of the findings and the assessment of long-term outcomes, such as relapse and steroid dependence. Multivariate analysis was not performed to assess possible confounding factors.

CONCLUSION

The initial response to steroid therapy is the main determinant of future disease course. Children who achieve remission later have high chances of experiencing subsequent relapses. Male sex, infections at presentation, hypertension at onset, and rural background were also associated with a higher risk of relapse. Haematuria and underlying malnutrition are important indicators of an unfavourable disease trajectory. Identifiable clinical features during the first episode can help predict relapse and guide follow-up planning. Late responders to steroid therapy should receive appropriate follow-up, and malnourished children

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should be counselled. Including time to remission along with these clinical predictors into routine evaluation will help in identifying high-risk patients early, optimising surveillance strategies, improving adherence, and minimising morbidity in paediatric nephrotic syndrome.

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