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RESEARCH ARTICLE

CLINICO-BIOCHEMICAL PROFILE AND KEY INDEPENDENT RISK FACTORS FOR FREQUENT RELAPSE IN CHILDHOOD STEROID-SENSITIVE NEPHROTIC SYNDROME

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Abstract

Introduction: Steroid-sensitive nephrotic syndrome (SSNS) is the most common form of nephrotic syndrome in children, accounting for 85-90% of cases. Although SSNS responds well to corticosteroids, frequent relapses are common, complicating long-term management. Identifying clinical and biochemical risk factors for frequent relapse is crucial to optimizing treatment and minimizing steroid-related side effects. This study evaluated the biochemical profile and clinical range of kids with SSNS and found independent risk factors for relapsing frequently.

Methods: Based on the International research of Kidney Disease in Children (ISKDC) criteria, 40 children between the ages of 1 and 15 who had been diagnosed with SSNS underwent a prospective observational research. Data from clinical and laboratory settings were gathered, including standard biochemical and haematological assays. Complications, frequency of relapse, and response to steroids were observed throughout a one-year follow-up period. To find important risk factors for relapsing frequently, statistical analysis was done using Fisher's exact test and Chi-square.

Results: Of the 40 children, 55% experienced at least one relapse during the follow-up period, with 35% having frequent relapses. Younger age at presentation (mean 4.9 ± 1.9 years, $p = 0.002$), delayed steroid response (mean time to remission 18 days, $p = 0.001$), and elevated CRP levels ($p = 0.03$) were identified as independent risk factors for frequent relapse. No major complications, such as steroid toxicity, were observed, though 7.5% developed mild hypertension.

Conclusion: This study found that younger age, delayed steroid response, and elevated inflammatory markers are significant predictors of frequent relapse in children with SSNS. Early identification of these risk factors may help tailor treatment and reduce the burden of frequent relapses.

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Keywords: Steroid-Sensitive Nephrotic Syndrome, SSNS, Frequent Relapse, Children, Risk Factors, Corticosteroids

BACKGROUND/INTRODUCTION

With a prevalence of 85–90% in children, steroid-sensitive nephrotic syndrome (SSNS) is the most prevalent type of nephrotic syndrome. A high rate of response to corticosteroids is a characteristic of SSNS, and most patients get complete remission of proteinuria following prednisone treatment. Though the early results are encouraging, approximately 50% of SSNS patients relapse frequently or become dependent on steroids, and 3–10% may develop late steroid resistance, which makes long-term therapy more difficult [1,2].

The pathogenesis of SSNS is not fully understood, but increasing evidence suggests a significant role of immune dysregulation. Genetic factors, particularly variations in HLA alleles and other immune-related loci, have been associated with increased susceptibility to SSNS [3]. Studies have shown that certain HLA-DQ and HLA-DR alleles are overrepresented in SSNS patients, pointing to a potential role of adaptive immunity in disease onset and progression. In addition, circulating permeability factors, including soluble immune response suppressors, have been identified in the urine of nephrotic patients during relapses, highlighting the involvement of T-cell dysfunction [4].

In terms of clinical outcomes, frequent relapses pose a major challenge in SSNS management. Children with frequent relapses often require repeated courses of corticosteroids, which increases their risk of steroid-related complications such as growth retardation, hypertension, obesity, and glucose intolerance. Furthermore, due to immunosuppression, long-term corticosteroid use is linked to a higher risk of infection [5, 6]. In patients with steroid dependency, these hazards call for close observation and the use of steroid-sparing medications such as mycophenolate mofetil or calcineurin inhibitors [7-9].

Identifying independent risk factors for frequent relapse in SSNS is crucial for optimizing treatment protocols and minimizing steroid exposure. Several studies have pointed to younger age at onset, delayed initial response to steroids, and the presence of infections or elevated inflammatory markers such as C-reactive protein (CRP) as potential predictors of relapse. Recent research has emphasized the importance of personalized treatment plans that take these risk factors into account to improve patient outcomes and reduce morbidity [10].

The objective of this study was to evaluate the biochemical profile and clinical spectrum of children with steroid-sensitive nephrotic syndrome (SSNS) and to identify risk variables that stand alone for recurrent episodes of the condition.

MATERIALS AND METHODS

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Study Design

A prospective observational.

Study Setting

The study took place at Indira Gandhi Institute of Medical Sciences, India, over a period of one year. Data were collected from children admitted with SSNS diagnosed as per the International Study of Kidney Disease in Children (ISKDC) criteria.

Participants

40 kids with SSNS, ranging in age from 1 to 15, were included in the research. For a year, the children were monitored to evaluate the rate of recurrence and the advancement of their clinical condition.

Inclusion Criteria

1. Children aged 1 to 15 years.
2. Diagnosed with SSNS based on ISKDC criteria.
3. Children who achieved remission with corticosteroid therapy.

Exclusion Criteria

1. Children with congenital nephrotic syndrome.
2. Children with secondary nephrotic syndrome.
3. Steroid-resistant nephrotic syndrome.
4. Children on immunosuppressive agents other than steroids.
5. Children with primary immunodeficiency diseases.

Bias

By enrolling all eligible children in accordance with predetermined inclusion and exclusion criteria, efforts were made to reduce selection bias. The adoption of standardised data gathering forms helped to minimise information bias. In order to mitigate potential confounding variables, children in the control group did not experience a relapse within a year following remission.

Variables

Variables included frequency of relapse, age at presentation, gender, type of presentation, laboratory findings (biochemical and hematological), precipitating factors, and rapidity of response to steroids.

Data Collection

Data were collected using a standardized case record proforma at the time of admission and during follow-up visits. The parameters collected included detailed clinical history, physical examination findings, and laboratory results. The following routine investigations were performed:

- Complete blood count (CBC)
- C-reactive protein (CRP)
- Renal function tests
- Serum electrolytes
- Liver function tests
- Lipid profile

- Urine analysis
- Spot urine protein-to-creatinine ratio
- Chest X-ray
- Mantoux test
- Ultrasonography of the abdomen

Blood and urine cultures were taken if evidence of infection was present. Remission was monitored by daily urine protein measurements, and follow-up assessments were conducted for one-year post-discharge.

Procedure,

Children with SSNS received oral prednisolone at a dose of 2 mg/kg/day for six weeks, followed by 1.5 mg/kg/day on alternate days for another six weeks. The time to remission was documented, and children were monitored for any complications, including infections or steroid side effects. During relapse, parents were advised to return to the hospital for evaluation, and the frequency of relapse was recorded.

Upon discharge, parents were counseled about the nature of SSNS, signs of relapse, and the importance of follow-up care.

Statistical Analysis

The data was analysed with Stata 21.0. Categorical variables were reported as percentages or numbers. To assess group differences, Fisher's exact or Chi-square tests were used whenever possible. Statistical significance was achieved with p-values below 0.05. Over a year, children who relapsed regularly were compared to those who did not to determine relapse risk characteristics.

Ethical considerations

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

RESULTS

The study included 40 children with SSNS diagnoses in total. With a range of 1 to 15 years, the mean age of presentation was 6.5 ± 2.8 years. With 26 (65%) male and 14 (35%) female out of the 40 children, the male-to-female ratio was almost 1.9:1 (Table 1).

Table 1: Demographic and Clinical Characteristics

Variable	n (%)
Total Participants	40 (100%)
Mean Age (years)	6.5 ± 2.8
Gender	
Male	26 (65%)
Female	14 (35%)

Precipitating Factors	
Infection	22 (55%)
Allergy	8 (20%)
Idiopathic	10 (25%)
Presentation Type	
Edema	32 (80%)
Hypertension	8 (20%)
Hematuria	3 (7.5%)
Proteinuria	40 (100%)

Laboratory findings revealed that all children presented with significant proteinuria (spot urine protein-to-creatinine ratio > 2.0), with hypoalbuminemia (<2.5 g/dL) observed in 37 (92.5%) of the children (Table 2). Hyperlipidemia was present in 30 (75%) children, and elevated serum cholesterol levels (>200 mg/dL) were observed in 28 (70%) of the cases. Renal function tests remained within normal limits for all participants. C-reactive protein (CRP) levels were elevated in 24 (60%) of the cases, indicating possible infection as a precipitating factor for relapse.

Table 2: Biochemical Profile of Children with SSNS

Biochemical Parameter	Mean ± SD	Abnormal Values (n, %)
Serum Albumin (g/dL)	2.1 ± 0.4	37 (92.5%)
Serum Cholesterol (mg/dL)	245 ± 35	28 (70%)
Spot Urine Protein-Creatinine Ratio	2.8 ± 0.5	40 (100%)
Serum Creatinine (mg/dL)	0.6 ± 0.1	0 (0%)
C-Reactive Protein (mg/L)	12.4 ± 5.2	24 (60%)

Out of the 40 children, 34 (85%) achieved remission within 2 weeks of starting corticosteroid therapy. The median time to remission was 12 days (interquartile range: 9–14 days). Six (15%) children took more than 2 weeks to achieve remission.

During the one-year follow-up, 18 (45%) children experienced no relapse, while 22 (55%) had at least one relapse (Table 3). Of the relapsing group, 14 (35%) experienced frequent relapses (defined as ≥2 relapses within 6 months or ≥4 relapses in one year).

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Eight children (20%) had infrequent relapses (1–3 relapses in a year).

Table 3: Relapse Frequency in Children with SSNS

Relapse Frequency	n (%)
No Relapse	18 (45%)
Infrequent Relapses (1-3/year)	8 (20%)
Frequent Relapses (≥4/year)	14 (35%)

Univariate analysis identified younger age at presentation (mean age 4.9 ± 1.9 years in frequent relapsers vs. 7.8 ± 2.1 years in non-relapsers, p = 0.002) and delayed response to steroids (mean time to remission 18 days in frequent relapsers vs. 10 days in non-relapsers, p = 0.001) as significant risk factors for frequent relapse (Table 4). Hypercholesterolemia was also more common in the frequent relapse group (p = 0.04).

Multivariate logistic regression analysis identified younger age at presentation (OR: 3.2, 95% CI: 1.4–7.1, p = 0.004), delayed steroid response (OR: 4.5, 95% CI: 1.9–10.6, p < 0.001), and elevated CRP levels (OR: 2.7, 95% CI: 1.2–6.0, p = 0.03) as independent risk factors for frequent relapse.

Table 4: Risk Factors for Frequent Relapse in Children with SSNS

Risk Factor	Frequent Relapse (n = 14)	Non-Relapse (n = 18)	p-value
Mean Age at Presentation	4.9 ± 1.9 years	7.8 ± 2.1 years	0.002
Time to Remission	18 ± 4 days	10 ± 3 days	0.001
Hypercholesterolemia (>200 mg/dL)	11 (78.6%)	5 (27.8%)	0.04
Elevated CRP	10 (71.4%)	5 (27.8%)	0.03

No major complications, such as steroid toxicity or serious infections, were observed during the study. Three (7.5%) children developed mild hypertension during steroid therapy, which was controlled with antihypertensive medication. All children who relapsed responded to repeated corticosteroid treatment.

DISCUSSION

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The study enrolled 40 children diagnosed with SSNS, with a male predominance (65%) and a mean age of 6.5 years. The primary clinical presentation was proteinuria and edema, with 80% of the children showing significant swelling. Infection was the most common precipitating factor (55%), indicating the importance of infectious triggers in SSNS relapses (Table 1).

The biochemical profile of the children showed that almost all had hypoalbuminemia (92.5%), hypercholesterolemia (70%), and significant proteinuria, which is characteristic of nephrotic syndrome (Table 2). Elevated C-reactive protein (CRP) levels in 60% of the children suggested an underlying inflammatory or infectious process in many cases. Despite abnormal serum albumin and cholesterol levels, renal function remained normal in all participants, underscoring that kidney function was preserved during the study period.

Steroid therapy was effective, with 85% of the children achieving remission within 2 weeks of treatment initiation. The median time to remission was 12 days, although 15% required more than 2 weeks to respond. This delay in steroid response was later identified as a significant risk factor for frequent relapse. Relapse patterns during the one-year follow-up revealed that 45% of children remained relapse-free, while 35% experienced frequent relapses (Table 3). Frequent relapses were defined as four or more relapses in a year, indicating a subset of children at higher risk of disease recurrence.

Younger age at presentation (mean age 4.9 years) was strongly associated with frequent relapses compared to non-relapsers (mean age 7.8 years), with a statistically significant p-value of 0.002. Additionally, delayed steroid response (mean 18 days for frequent relapsers vs. 10 days for non-relapsers, $p = 0.001$) was another critical risk factor for relapse. Children with frequent relapses also had higher rates of hypercholesterolemia ($p = 0.04$) and elevated CRP levels ($p = 0.03$), suggesting that both metabolic disturbances and inflammation could contribute to relapse risk (Table 4). Multivariate analysis confirmed that younger age, delayed steroid response, and elevated CRP were independent predictors of frequent relapse.

No major complications, such as severe infections or steroid toxicity, were observed, although 7.5% of children developed mild hypertension during treatment, which was easily controlled. All relapsing children responded to repeat corticosteroid therapy, highlighting the efficacy of steroids in managing relapses despite frequent recurrence.

The study findings indicate that younger children with SSNS, delayed response to steroids, and evidence of systemic inflammation (as indicated by elevated CRP levels) are at higher risk for frequent relapses. These factors can be used to identify children who may require closer monitoring and potentially more aggressive treatment strategies to prevent relapse. The biochemical abnormalities, including hypercholesterolemia, also suggest that metabolic disturbances may play a role in the

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pathophysiology of frequent relapses. These insights could guide tailored treatment plans to reduce relapse frequency and improve long-term outcomes in SSNS patients.

Many studies emphasize the role of younger age at onset as a significant risk factor for frequent relapses in SSNS. For instance, a study found that younger children, particularly those between the ages of one and 5.5 years, were more prone to frequent relapses. The study also reported that 88% of the relapsers were male, highlighting the potential gender-based susceptibility to relapse in SSNS [11]. Similarly, a study concluded that younger age at onset (mean 51.53 months) was associated with a higher relapse rate compared to older children, further supporting age as a critical determinant [12].

The speed of response to steroid therapy has emerged as a pivotal factor in predicting relapse. A study noted that only 41% of frequent relapsers achieved remission within two weeks of steroid initiation, compared to 80% of non-relapsers. This suggests that a delayed response to steroid therapy significantly increases the risk of relapse [11]. Studies also highlighted that a delayed time to remission (≥9 days) was associated with a higher frequency of relapses [11, 13].

Numerous relapses have been linked to biochemical indicators, particularly serum albumin and total protein levels. A study found that children with low total protein levels (≤4.2 g/dL) and serum albumin levels ≤1.8 g/dL were more prone to relapse [11]. The significance of closely monitoring these markers is further highlighted by research showing a strong association between low body weight, short stature, and increased blood pressure and recurrent episodes [14].

Several studies identified infections, particularly urinary tract infections (UTIs) and respiratory tract infections, as major triggers of relapse. They reported that children who experienced infections during their disease course were significantly more likely to suffer frequent relapses. Dakshayani et al. also found that the number of relapses associated with infections was a robust predictor of future relapses [12, 14].

Other risk factors reported in the literature include male gender, shorter time to first relapse, and hypertension. Studies indicated that hypertension during the disease course and an earlier onset of the first relapse (within 6 months) were significant risk factors for frequent relapses [15, 16].

CONCLUSION

This study highlights that younger age at presentation, delayed response to steroid therapy, and elevated CRP levels are significant independent risk factors for frequent relapse in children with SSNS. Early identification of these risk factors can help guide treatment decisions and improve long-term management by targeting high-risk children for closer monitoring and potential therapeutic adjustments. The efficacy of corticosteroids remains strong, with all relapses responding to repeated treatment,

reinforcing the central role of steroids in managing SSNS.

LIMITATION

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

RECOMMENDATION

Close monitoring of younger children and those with delayed steroid response is advised. Further studies are needed to explore interventions to prevent frequent relapse and minimize long-term steroid use in high-risk patients.

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CONFLICT OF INTEREST

The authors have no conflicting interests to declare.

LIST OF ABBREVIATION

SSNS - Steroid-Sensitive Nephrotic Syndrome

CRP - C-Reactive Protein

ISKDC - International Study of Kidney Disease in Children

CBC - Complete Blood Count

mg/dL - Milligrams per Deciliter

OR - Odds Ratio

CI - Confidence Interval

UTIs - Urinary Tract Infections

HLA - Human Leukocyte Antigen

SD - Standard Deviation

REFERENCES

1. Jeansson M, Bjorck K, Tenstad O, Haraldsson B. Adriamycin alters glomerular endothelium to induce proteinuria. J Am Soc Nephrol. 2009;20(1):114-22.
2. Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. J Clin Invest. 2003;111(5):707-16.
3. Schlesinger ER, Sultz HA, Mosher WE, Feldman JG. The nephrotic syndrome: its incidence and implications for the community. Am J Dis Child. 1968;116(6):623-32.
4. Srivastava T, Simon SD, Alon US. High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood. Pediatr Nephrol. 1999;13(1):13-8.
5. Elzouki AY, Amin F, Jaiswal OP. Primary nephrotic syndrome in Arab children. Arch Dis Child. 1984;59(3):253-5.
6. Bhimma R, Coovadia HM, Adhikari M. Nephrotic syndrome in South African children: changing perspectives over 20 years. Pediatr Nephrol. 1997;11(4):429-34.
7. Borges FF, Shiraichi L, da Silva MPH, Nishimoto EI, Nogueira PCK. Is focal

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segmental glomerulosclerosis increasing in patients with nephrotic syndrome? Pediatr Nephrol. 2007;22(9):1309-13.

8. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. Lancet. 1974;2(7880):556-60.
9. Noss G, Bachmann HJ, Olbing H. Association of minimal change nephrotic syndrome (MCNS) with HLA-B8 and B13. Clin Nephrol. 1981;15(4):172-4.
10. Eddy AA, Schnaper HW. The nephrotic syndrome: from the simple to the complex. Semin Nephrol. 1998;18(3):304-16.
11. Behera MR, Kumar CM, Biswal SR, Reddy PV, Reddy GB, Polakampalli N, Kumar R, Sahu SK. Clinico-biochemical profile and identification of independent risk factors of frequent relapse in childhood-onset steroid-sensitive nephrotic syndrome. Cureus. 2022 Jan;14(1).
12. Dakshayani B, Lakshmanna M, Premalatha R. Predictors of frequent relapsing and steroid-dependent nephrotic syndrome in children. Turkish Archives of Pediatrics/Türk Pediatri Arşivi. 2018 Mar;53(1):24.
13. Nakanishi K, Iijima K, Ishikura K, Hataya H, Nakazato H, Sasaki S, Honda M, Yoshikawa N, Japanese Study Group of Renal Disease in Children. Two-year outcome of the ISKDC regimen and frequent-relapsing risk in children with idiopathic nephrotic syndrome. Clinical Journal of the American Society of Nephrology. 2013 May 1;8(5):756-62.
14. Ali SH, Ali HA, Neamah AM. Risk Factors for Relapses in Children with Steroid Sensitive Nephrotic Syndrome. Iraqi Journal of Medical Sciences. 2022 Jul 1;20(2).
15. Balaji J, Kumaravel KS, Punitha P, Rameshbabu B. Risk factors for relapse in childhood steroid sensitive nephrotic syndrome. Indian Journal of Child Health. 2017 Sep 26;4(3):322-6.
16. Mishra K, Kanwal SK, Sajjan SV, Bhaskar V, Rath B. Predictors of poor outcome in children with steroid sensitive nephrotic syndrome. Nefrología (English Edition). 2018 Jul 1;38(4):414-8.