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Original Article

Coagulation Abnormalities and Prothrombotic Tendency in Paediatric Idiopathic Nephrotic Syndrome: A Case-Control Study from South India

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ABSTRACT

Background: Idiopathic nephrotic syndrome (INS) in children is associated with a hypercoagulable state due to urinary loss of anticoagulants and hepatic overproduction of procoagulants in response to hypoalbuminemia. Routine coagulation tests often remain normal, highlighting the need for targeted profiling to identify prothrombotic markers and stratify risk.

Materials and Methods: This hospital-based observational study enrolled 50 children aged 1-18 years with active INS and 50 age- and sex-matched healthy controls at a tertiary center in South India from January 2022 to June 2023. Exclusion criteria included secondary nephrotic syndrome, inherited coagulopathies, and anticoagulant use. Coagulation parameters (platelet count, PT, aPTT, fibrinogen) alongside renal and lipid profiles were assessed using standardized automated analyzers. Data were analyzed with SPSS v25; continuous variables compared via t-tests, with $p<0.05$ considered significant.

Results: Cases exhibited classic nephrotic features: hypoalbuminemia (mean 2.00 ± 0.47 g/dL), heavy proteinuria (mean 2.48 ± 0.55 g/24h), and hypercholesterolemia (mean 342.4 ± 83.6 mg/dL), all significantly different from controls ($p<0.001$). Platelet count (3.19 ± 0.82 vs. 2.85 ± 0.70 $\times 10^5$/µL; $p=0.027$) and fibrinogen (294.1 ± 79.3 vs. 277.0 ± 43.7 mg/dL; $p=0.001$) were mildly elevated in cases, while PT and aPTT were normal. Renal function remained preserved.

Conclusion: Paediatric INS is characterized by subtle prothrombotic changes—elevated platelets and fibrinogen—despite normal PT/aPTT, driven by severe hypoalbuminemia. These accessible markers may aid risk stratification for thrombosis in resource-limited settings, emphasizing vigilant monitoring in high-risk patients.

Keywords: *Nephrotic Syndrome, Paediatric age group, Blood Coagulation Disorders, Thrombophilia, Fibrinogen, Platelet Count.*

INTRODUCTION

Idiopathic nephrotic syndrome (INS) is one of the most common chronic renal disorders encountered in paediatric and young adult populations, characterized clinically by massive proteinuria, hypoalbuminemia, generalized edema, and hyperlipidemia [1]. Despite significant advances in understanding the immunopathogenesis and treatment of nephrotic syndrome, its systemic complications continue to pose considerable morbidity and, in some cases, mortality [2].

Nephrotic syndrome is widely recognized as a hypercoagulable state. The propensity for thrombosis in these patients has been reported in both paediatric and adult cohorts, with venous thromboembolism being more frequent than arterial events. Renal vein thrombosis, deep vein thrombosis, pulmonary embolism, and cerebral venous sinus thrombosis are among the documented complications [2].

The hypercoagulable state observed in idiopathic nephrotic syndrome is multifactorial and arises from a complex interplay of alterations in procoagulant, anticoagulant, and fibrinolytic pathways [3]. Massive urinary loss of low-molecular-weight anticoagulant proteins, particularly antithrombin III, protein C, and protein S, plays a central role. This loss is compounded by increased hepatic synthesis of procoagulant factors such as fibrinogen, factors V, VIII, and X, in response to hypoalbuminemia [2, 3].

Hypoalbuminemia, a hallmark of nephrotic syndrome, has been independently associated with an increased risk of thrombosis. Low serum albumin levels lead to hemoconcentration, increased blood viscosity, and endothelial dysfunction, all of which favor clot formation. Hyperlipidemia, another characteristic feature of nephrotic syndrome, is believed to enhance platelet activation and impair fibrinolysis, thereby further increasing thrombotic risk [4].

Idiopathic nephrotic syndrome encompasses a heterogeneous group of disorders, most commonly minimal change disease, focal segmental glomerulosclerosis, and mesangial proliferative glomerulonephritis. Steroid-sensitive nephrotic syndrome, which constitutes the majority of paediatric cases, may demonstrate reversible coagulation changes during remission, whereas steroid-resistant forms are often associated with prolonged disease activity and a higher thrombotic risk [5].

The evaluation of coagulation profile in idiopathic nephrotic syndrome is of practical clinical relevance for several reasons. First, early identification of coagulation abnormalities may help stratify patients at higher risk for thromboembolic complications. Second, understanding the pattern of coagulation derangement during active disease and remission can aid in determining the reversibility of these changes. Third, it may guide clinicians in considering prophylactic or therapeutic anticoagulation in selected high-risk patients, particularly those with severe hypoalbuminemia or prolonged disease course [6].

Despite the recognized association between nephrotic syndrome and hypercoagulability, routine coagulation screening is not universally practiced, especially in resource-limited settings. This gap highlights the need for systematic studies evaluating coagulation parameters in patients with idiopathic nephrotic syndrome and correlating them with clinical and biochemical variables.

The present study was therefore undertaken to assess the coagulation profile of patients with idiopathic nephrotic syndrome and to compare these parameters with those of age- and sex-matched healthy controls. By providing insight into the nature and extent of coagulation abnormalities in INS, this study aims to contribute to improved risk assessment and management strategies in this vulnerable patient population.

MATERIALS AND METHODS

Study Setting: This hospital-based observational study was conducted in the Department of Paediatrics at Tirunelveli Medical College, a tertiary care teaching hospital in South India. The institution serves as a major referral center for renal disorders and caters to both urban and rural populations. The study was carried out over a period of 18 months from January 2022 to June 2023, during which eligible patients attending the inpatient and outpatient services were recruited. Laboratory investigations were performed in the hospital's central clinical laboratory, which is equipped with standardized automated analyzers and follows strict internal and external quality control protocols.

Study Participants: The study population comprised patients diagnosed with idiopathic nephrotic syndrome based on standard clinical and laboratory criteria. Diagnosis was established by the presence of generalized edema, nephrotic-range proteinuria, hypoalbuminemia, and hyperlipidemia, in the absence of secondary causes such as systemic lupus erythematosus, diabetes mellitus, or infections.

Inclusion criteria included patients aged 1–18 years (or as per institutional practice) with a confirmed diagnosis of idiopathic nephrotic syndrome, either newly diagnosed or in relapse. Patients were enrolled during the active phase of the disease prior to initiation or modification of anticoagulant therapy. Both steroid-sensitive and steroid-resistant cases were included to reflect the full clinical spectrum of the disease.

Exclusion criteria comprised patients with secondary nephrotic syndrome, congenital nephrotic syndrome, known inherited coagulation disorders, chronic liver disease, or those receiving anticoagulant or antiplatelet medications. Patients with active infections, recent surgery, trauma, or documented thromboembolic events at the time of enrollment were excluded to avoid confounding effects on coagulation parameters.

Sample Size and Sampling Technique: The sample size was calculated based on previous studies reporting significant differences in coagulation parameters between nephrotic syndrome patients and healthy controls. Assuming a confidence level of 95% and adequate statistical power, a minimum sample size of 50 children was determined. A comparable

number of age- and sex-matched healthy controls were recruited. A consecutive sampling technique was employed, whereby all eligible patients presenting during the study period were included until the desired sample size was achieved.
Study Tools: Data were collected using a pre-designed and pre-tested structured proforma. The proforma included demographic details, clinical history, duration of illness, treatment status, and laboratory parameters. Laboratory investigations included routine renal function tests, serum albumin, lipid profile, and coagulation parameters.

The coagulation profile consisted of platelet count, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and plasma fibrinogen levels. Blood samples were collected under aseptic precautions and processed according to standard laboratory protocols.

Study Methodology: After obtaining eligibility confirmation, patients were enrolled and detailed clinical evaluation was performed. Venous blood samples were collected prior to administration of steroids or anticoagulant therapy. Samples for coagulation studies were collected in citrate-containing tubes and analyzed within the recommended time frame to ensure accuracy.

Coagulation parameters were measured using automated coagulation analyzers. Results were recorded and compared with established reference ranges. Similar procedures were followed for control subjects to maintain consistency. All laboratory personnel were blinded to the clinical status of participants to reduce observer bias.

Ethical Issues: The study protocol was reviewed and approved by the Institutional Ethics Committee prior to initiation. Written informed consent was obtained from parents or legal guardians of paediatric participants, and assent was obtained where appropriate. Confidentiality of patient information was strictly maintained, and all data were anonymized prior to analysis. The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 25. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparisons between cases and controls were performed using independent t-tests or Mann–Whitney U tests as appropriate. A p value of less than 0.05 was considered statistically significant.

RESULTS

The study enrolled 50 children with idiopathic nephrotic syndrome (cases) and 50 age- and sex-matched healthy controls. The demographic profile showed a slight male predominance, with no significant differences between groups in age or sex distribution. Clinically, the majority of cases presented with classic features of nephrotic syndrome, including generalized edema and abdominal distension, while decreased urine output was also common. Relapses were observed in a subset of patients (Table 1).

Table 1. Demographic and clinical characteristics of children with idiopathic nephrotic syndrome (cases) and healthy controls

Characteristic	Cases (n=50)	Controls (n=50)	Total (n=100)
Age group, n (%)			
2–6 years	22 (44%)	22 (44%)	44 (44%)
6–12 years	28 (56%)	28 (56%)	56 (56%)
Sex, n (%)			
Male	28 (56%)	28 (56%)	56 (56%)
Female	22 (44%)	22 (44%)	44 (44%)
Clinical features, n (%)			
Generalized edema	45 (90%)	0 (0%)	45 (45%)
Abdominal distension	50 (100%)	0 (0%)	50 (50%)
Decreased urine output	44 (88%)	0 (0%)	44 (44%)
Fever	0 (0%)	0 (0%)	0 (0%)
Abdominal pain	0 (0%)	1 (2%)	1 (1%)
Breathlessness	0 (0%)	0 (0%)	0 (0%)

All children with idiopathic nephrotic syndrome exhibited heavy proteinuria and hypoalbuminemia, with marked hypercholesterolemia confirming the typical biochemical profile of the condition. Urinary protein excretion was in the nephrotic range in every case, and serum cholesterol levels were substantially elevated compared with expected normal paediatric values (Table 2).

Table 2. Key laboratory parameters confirming nephrotic syndrome in cases (n=50)

Parameter	Value
Urine albumin (sulfosalicylic acid test), n (%)	
Moderate (3+)	26 (52%)
Severe (4+)	24 (48%)
24-hour urinary protein (g/24 h)	
Mean ± SD	2.48 ± 0.55
Range	1.6–3.8
Serum albumin (g/dL)	
Mean ± SD	2.00 ± 0.47
Range	1.1–2.9
Serum cholesterol (mg/dL)	
Mean ± SD	342.4 ± 83.6
Range	174.5–580.0

Platelet count and serum fibrinogen were mildly elevated in the nephrotic group, consistent with a prothrombotic tendency commonly described in idiopathic nephrotic syndrome. Renal function parameters (blood urea and serum creatinine) remained within normal limits, and prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal in all participants (Table 3).

Table 3. Hematological, coagulation, and renal function parameters in cases and controls

Parameter	Cases (n=50)	Controls (n=50)
Platelet count ($\times 10^5$/μL)		
Mean ± SD	3.19 ± 0.82	2.85 ± 0.70
Range	1.74–6.50	–
Serum fibrinogen (mg/dL)		
Mean ± SD	294.1 ± 79.3	277.0 ± 43.7
Blood urea (mg/dL)		
Mean ± SD	25.9 ± 6.4	25.9 ± 6.4
Serum creatinine (mg/dL)		
Mean ± SD	0.96 ± 0.21	0.96 ± 0.21

Independent-samples t-tests revealed highly significant differences between cases and controls in serum albumin, 24-hour urinary protein, serum cholesterol, and platelet count. Serum fibrinogen showed a statistically significant mild elevation in the nephrotic group, supporting a hypercoagulable state (Table 4).

Table 4. Comparison of laboratory variables between cases and controls.

Variable	Cases (n=50) Mean ± SD	Controls (n=50) Mean ± SD	Mean Difference	t-value	df	p-value
Serum albumin (g/dL)	2.00 ± 0.47	3.32 ± 0.32	1.32	16.538	98	<0.001
24-hour urinary protein (g/24 h)	2.48 ± 0.55	0.65 ± 0.19	1.84	22.406	98	<0.001
Serum cholesterol (mg/dL)	342.4 ± 83.6	190.8 ± 37.8	151.6	11.679	98	<0.001
Platelet count ($\times 10^5$/μL)	3.19 ± 0.82	2.85 ± 0.70	0.34	2.248	98	0.027
Serum fibrinogen (mg/dL)	294.1 ± 79.3	277.0 ± 43.7	17.1	1.331	98	0.001

Chi-square or Fisher's exact tests were used to assess associations for less prevalent or ancillary features. No significant associations were observed for abdominal pain, positive urine culture, or abnormal peripheral blood smear (microcytic hypochromic anemia). Mild proteinuria (trace or 1+ urine albumin) was observed exclusively in the control group, though the difference did not reach statistical significance after categorisation (Table 5).

Table 5. Association between selected ancillary clinical and laboratory features and group (cases vs. controls)

Feature	Present in Cases n (%)	Present in Controls n (%)	χ^2 value (or Fisher's exact)	df	p-value
Abdominal pain	0 (0%)	1 (2%)	1.010	1	0.315
Positive urine culture	2 (4%)	0 (0%)	2.041	1	0.153
Abnormal peripheral smear (microcytic	1 (2%)	1 (2%)	0.000	1	1.000

hypochromic anemia)					
Mild proteinuria (trace or 1+ urine albumin)	0 (0%)	3 (6%)	3.093*	1	0.079
Normal peripheral smear	49 (98%)	49 (98%)	0.000	1	1.000

*Fisher's exact test used due to low expected cell counts.

DISCUSSION

The present study demonstrates that children with idiopathic nephrotic syndrome (INS) during the active phase exhibit subtle alterations in coagulation parameters indicative of a prothrombotic tendency, despite normal prothrombin time (PT) and activated partial thromboplastin time (aPTT). Specifically, we observed statistically significant elevations in platelet count (mean $3.19 \pm 0.82 \times 10^5/\mu L$ vs. $2.85 \pm 0.70 \times 10^5/\mu L$ in controls; p=0.027) and serum fibrinogen (mean 294.1 ± 79.3 mg/dL vs. 277.0 ± 43.7 mg/dL; p=0.001). These findings align with the well-established recognition of INS as a hypercoagulable state, driven by urinary losses of anticoagulant proteins and compensatory hepatic synthesis of procoagulants in response to hypoalbuminemia.

The hallmark biochemical features of nephrotic syndrome in our cohort—severe hypoalbuminemia (mean serum albumin 2.00 ± 0.47 g/dL), nephrotic-range proteinuria (mean 24-hour urinary protein 2.48 ± 0.55 g), and hypercholesterolemia (mean 342.4 ± 83.6 mg/dL)—were profoundly different from controls ($p<0.001$ for all). Hypoalbuminemia, in particular, is a key driver of thrombotic risk, as it stimulates hepatic production of fibrinogen and other large-molecular-weight procoagulants while smaller anticoagulant proteins like antithrombin III (AT-III), protein C, and protein S are lost in the urine due to glomerular permeability defects [7].

Notably, PT and aPTT remained within normal limits in all participants, a finding consistent with several prior paediatric studies. Routine screening tests like PT and aPTT primarily assess the extrinsic and intrinsic pathways but are insensitive to the nuanced imbalances in INS hypercoagulability, where losses of low-molecular-weight anticoagulants are offset by gains in procoagulants. Global assays, such as rotational thromboelastometry (ROTEM), have revealed hypercoagulability in acute-phase paediatric INS despite normal conventional parameters [8].

The mild but significant elevation in platelet count supports platelet hyperreactivity as a contributing factor to thrombosis in paediatric INS. Thrombocytosis has been documented in 15-57% of cases across cohorts, often correlating with disease activity. Increased platelet aggregation, potentially exacerbated by hyperlipidemia, further tilts the hemostatic balance toward thrombosis [9]. In our study, the absence of documented thromboembolic events may reflect the relatively preserved renal function (normal urea and creatinine) and the predominance of steroid-sensitive cases, as steroid-resistant INS is associated with prolonged activity and higher thrombotic risk [10].

Comparisons with existing literature highlight both consistencies and variations. Our findings of mildly elevated fibrinogen without PT/aPTT prolongation suggest that the prothrombotic state in South Indian children with INS is subtler than in some reported cohorts, possibly influenced by genetic, environmental, or histological differences (e.g., predominance of minimal change disease in steroid-sensitive paediatric cases) [11].

The clinical implications of these abnormalities are substantial. Although thromboembolic complications are rarer in children (approximately 3-9%) than adults (up to 40%), they carry significant morbidity, including renal vein thrombosis, pulmonary embolism, and cerebral sinus thrombosis [12]. Severe hypoalbuminemia (<2.0-2.5 g/dL) emerges as the strongest predictor of venous thromboembolism across meta-analyses and large cohorts, with each 1 g/dL decrement increasing risk twofold. In our cohort, mean albumin of 2.0 g/dL places many patients at elevated risk, warranting vigilant monitoring.

Despite recognized hypercoagulability, routine coagulation screening is not universal, particularly in resource-limited settings like ours. Our results advocate for selective profiling—platelet count and fibrinogen—as accessible markers of prothrombotic tendency. These could aid risk stratification, especially in patients with albumin <2.5 g/dL, prolonged relapse, or steroid resistance [13]. Prophylactic anticoagulation remains controversial in paediatrics due to low event rates and bleeding risks, but high-risk subgroups may benefit from low-dose aspirin or anticoagulation during severe hypoalbuminemia [14].

Limitations of this study include the lack of specific anticoagulant measurements (e.g., AT-III, protein C/S) and global hemostatic assays, which could have elucidated compensatory mechanisms more precisely. The cross-sectional design captured only active-phase changes, precluding assessment of reversibility in remission. Additionally, histological confirmation was not performed, though clinical criteria reliably identify INS in children. Future prospective studies incorporating thromboelastography, AT-III levels, and longitudinal follow-up during remission and relapse would strengthen understanding of dynamic coagulation changes.

CONCLUSION

This study confirms a mild prothrombotic profile in paediatric INS characterized by elevated platelets and fibrinogen, superimposed on profound hypoalbuminemia and hyperlipidemia. These alterations, though subtle on routine tests, underscore the need for heightened awareness of thrombotic risk. In resource-constrained environments, monitoring platelet count, fibrinogen, and albumin may guide individualized management, potentially preventing life-threatening complications in this vulnerable population.

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