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ORIGINAL ARTICLE

Clinical presentations and outcomes of congenital and infantile nephrotic syndrome.

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ABSTRACT… Objective: To describe the characteristics and outcomes of congenital nephrotic syndrome (CNS) and infantile nephrotic syndrome (INS). **Study Design:** Cross-sectional study. **Setting:** Department of Pediatric Nephrology, National Institute of Child Health, Karachi, Pakistan. **Period:** July 2023 to January 2024. **Methods:** All cases of CNS or INS visiting the outpatient, emergency department, or admitted in Nephrology ward were analyzed. Data including demographic characteristic and anthropometric measurements, clinical history and presentation were noted. Short-term outcomes in terms of cases who were discharged from hospital or those who died were recorded. **Results:** In a total of 33 infants, 17 (51.5%) were male. The mean age was 5.8±3.2 months. The mean days from onset of edema to the time of enrollment was 33.27±22.63 days. The most common presenting features were ascites noted in 4 (12.1%). Associated infections were reported in 21 (63.6%) infants. INS and CNS were noted in 25 (75.8%) and 8 (24.2%) infants respectively. Mortality was reported in 11 (33.3%) infants. **Conclusion:** Infections were the most common associated conditions in congenital and infantile nephrotic syndrome. Short term outcomes exhibiting high mortality rates warrants early identification and treatment of congenital and infantile nephrotic syndrome.

Key words: Ascites, Edema, Infection, Mortality, Nephrotic Syndrome.

INTRODUCTION

Nephrotic syndrome (NS) is recognized as a prevalent chronic ailment in pediatric populations, with minimal changed disease standing out as the most prevalent histological type.[1] Congenital nephrotic syndrome (CNS) manifests within the first 3 months of life, while infantile nephrotic syndrome (INS) typically emerges between 3-12 months post-birth.[2] Both conditions contribute significantly to morbidity. Characterized by edema, hyperlipidemia, and hypercoagulable states, CNS and INS bring about substantial health challenges.[3,4] CNS is linked to various syndromes, including “Denys–Drash syndrome”, “Galloway–Mowat syndrome”, “Pierson syndrome”, and “nail–patella syndrome”.[5]

The treatment of NS may involve the utilization of anti-proteinuric options, including “renin-angiotensin-aldosterone system (RAAS)” inhibitors and “nonsteroidal anti-inflammatory drugs” (NSAIDs such as indomethacin). Intravenous albumin infusions, with or without diuretic administration, along with aggressive nutritional supplementation (130 kcal/kg/day), are commonly employed.[6,7] In the case of Congenital Nephrotic Syndrome (CNS), resistance to corticosteroids and immunosuppressive drugs is often observed due to its non-immunological pathogenesis. Management strategies for CNS focus on edema control, complication prevention, and adequate nutrition; however, kidney transplantation is frequently necessary in most cases.[8] Regarding Infantile Nephrotic Syndrome (INS), a typical approach involves combined treatment with steroids and immunosuppressants.[9]

NS is a chronic relapsing disease with long-term outcomes but CNS and INS are generally associated with relatively poor outcomes.[10] Tthe present observational study aimed to shed light on the characteristics and outcomes of CNS and INS. The findings of the present study are thought

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to add important insights about what is already known about the characteristics and outcomes of CNS and INS in Pakistan. The objective of this study was to describe the characteristics and outcomes of CNS and INS.

METHODS

This cross-sectional study was performed at the department of Pediatric Nephrology, "National Institute of Child Health (NICH)", Karachi, Pakistan from July 2023 to January 2024. It was not possible to calculate the exact sample size for this research as CNS and INS are not very commonly reported. Non-probability consecutive sampling technique. We considered all CNS and INS cases presenting during the study period for this research. Inclusion criteria were cases of CNS or INS visiting the outpatient, emergency department, or admitted in Nephrology ward. Children having NS above 12 months of age were excluded. Parents or caregivers of infants unwilling to be part of this study were excluded. NS was defined as "urine protein/creatinine ratio ≥ 2.0, serum albumin ≤2.5 g/dL, high serum cholesterol, and peripheral edema". CNS was labeled as cases presenting at 3 months or less than 3 months of age. INS was described as cases presenting from more than 3 months to 12 months of age.

Approval from Institutional Ethical Review Board (IERB), NICH was obtained (IERB-52/2023). All children were enrolled after written consent from parents/caregivers. Data including demographic characteristic and anthropometric measurements, clinical history and presentation were noted. The medical history of Cytomegalovirus (CMV), syphilis, toxoplasmosis, rubella, HBV and HIV infection during the pregnancy were asked. Family history of kidney disease was also noted. All workup including lab investigations were done free of cost at NICH lab, however TORCH profile to rule out secondary causes of CNS if needed were sent outside the study institute. If patients could not afford outside investigations, the investigators helped in bearing the costs. All patients were managed routinely according to hospital protocol. Parents/guardian was counseled regarding possible poor prognosis and outcomes. Patients with renal failure were managed conservatively in department rather than by long-term dialysis. Temporary peritoneal dialysis was offered to selected patients whose parents/guardian were willing for this mode of treatment after proper counselling by pediatric nephrologist and his/her team. Glomerular Filtration Rate will be calculated by Schwartz formula: Where k=0.33 in low birth weight, 0.45 in infants <1year, 0.55 after 1 yrs. L is length/height in cm and Pcr is plasma creatinine level (mg/dl). Short-term outcomes in terms of cases who were discharged from hospital or those who died were recorded.

The data analysis was conducted using "IBM-SPSS Statistics," version 26.0. Qualitative data were presented as frequencies and percentages, while quantitative variables were expressed as mean and standard deviation (SD). To control for effect modifiers, stratification was employed, and post-stratification chi-square tests or independent sample t-tests were utilized to compare their impact on outcomes taking $p<0.05$ as significant.

RESULTS

In a total of 33 infants, 17 (51.5%) were male. The mean age was 5.8±3.2 months. The mean weight and height were calculated to be 6.07±2.01 kg and 62.42±7.08 cm respectively. The mean body sufrace area was 0.31±0.07 m^2. The mean systolic and diastolic blood pressure were 103.14±17.57 mmHg and 61.43±18.32 mmHg respectively. The mean days from onset of edema to the time of enrollment was 33.27±22.63 days. The mean birth weight was 2.42±0.46 kg and the mean placental weight at the time of birth was 651.43±100.24 grams. The most common presenting features were ascites noted in 4 (12.1%). Associated infections were reported in 21 (63.6%) infants. INS and CNS were noted in 25 (75.8%) and 8 (24.2%) infants respectively (24.2%).

Table-II is showing comparison of various laboratory parameters evaluated in CNS and INS cases.

Mortality was reported in 11 (33.3%) infants. Comparison of study variables with respect to

outcomes are shown in Table-III and infants leaving against medical advice were not included in this analysis.

Characteristics		Frequency (%)
Gender	Male	17 (51.5%)
	Female	16 (48.5%)
Age (months)	≤3	8 (24.2%)
	>3 to 12	25 (75.8%)
Consanguinity		16 (48.5%)
Family history of kidney diseases		4 (12.1%)
Ascites		4 (12.1%)
Dysmorphic features		2 (6.1%)
Associated infections		21 (63.6%)
Nephrotic syndrome	Congenital	8 (24.2%)
	Infantile	25 (75.8%)

Table-I. Baseline characteristics (n=33)

DISCUSSION

In this study, 51.5% infants with NS were male showing relatively similar gender distribution. A study by Okpere et al from Canada reported that 60% of children with NS were male.[11] Some others have also shown male dominance.[12] A study evaluating 69 children, 59% were females among CNS cases while 55% females formed INS cases.

One of the key clinical findings in our study was notable proportion of associated infections, observed in 63.6% infants. This finding underscores the significance of timely identification and treatment of associated infections in the manifestation of NS. The prevalence of associated infections (63.6%) is notably higher than what was reported by 43.8% hospitalized NS children suggesting a potential variation in disease manifestation across different populations.[14] Individuals with NS face an elevated susceptibility to infections.

Parameters	Total (N=33)	Congenital nephrotic syndrome (n=8)	Infantile nephrotic syndrome (n=25)	P-Value
Total leukocyte count (x10^9/l)	16.96±±9.81	21.15±15.46	15.56±6.98	0.166
Neutrophil count (%)	54.17±22.92	59.50±26.98	52.83±22.50	0.533
Lymphocyte count (%)	38.50±15.71	38.67±21.13	38.45±14.53	0.977
Creatinine (mg/dl)	0.63±0.90	1.25±1.60	0.43±0.36	0.023
Urea (mg/dl)	34.16±28.77	50.25±38.07	28.79±23.55	0.067
Albumin (g/dl)	1.58±0.30	1.46±0.33	1.61±0.29	0.234
Cholesterol (mg/dl)	295.90±99.25	289.83±111.75	297.36±98.49	0.871
TSH (mIU/mL)	9.22±5.12	10.82±5.66	6.00±0.92	0.129
T3 (ug/dL)	2.16±0.20	2.02±0.21	2.30±0.20	0.002
T4 (ug/dL)	4.93±1.97	4.06±1.84	6.65±0.52	0.023
Protein/creatinine ratio	2.87±0.34	11.88±5.09	10.37±8.41	0.659

Table-II. Laboratory parameters in congenital and infantile nephrotic syndrome

Characteristics		Outcome		
		Discharged (n=17)	Expired (n=11)	P-Value
Gender	Male	10 (58.8%)	6 (54.5%)	0.823
	Female	7 (41.2%)	5 (45.5%)	
Age (months)	≤3	3 (17.6%)	5 (45.5%)	0.112
	>3 to 12	14 (82.4%)	6 (54.5%)	
Consanguinity		11 (64.7%)	4 (36.4%)	0.142
Family history of kidney diseases		2 (11.8%)	-	0.238
Ascites		2 (11.8%)	-	0.238
Dysmorphic features		-	2 (18.2%)	0.068
Associated infections		11 (64.7%)	6 (54.5%)	0.591
Nephrotic syndrome	Congenital	3 (17.6%)	5 (45.5%)	0.112
	Infantile	14 (82.4%)	6 (54.5%)	

Table-III. Comparison of study variables with respect to outcomes (N=28)

While the incidence of infections in NS has diminished in developed nations, it remains a significant concern in developing countries.[15] Experts recommend treating patients with infection-related NS using specific antimicrobial agents and conducting genetic screening in these cases.[16,17] The consensus recommendations from "ERKNet-ESPN Working Group", however, do not include guidance on the use of prophylactic antibiotics or intravenous immunoglobulin (IVIG).[18]

The present study reported high mortality rate (33.3%) in congenital and infantile NS. Prior to the discovery of glucocorticoids as an efficacious treatment for inducing remission in the 1950s, childhood NS was linked with a considerable mortality rate of approximately 40%.[19] This high mortality was attributed to various complications such as AKI, chronic kidney disease (CKD), systemic infections, and thromboembolic events.[20] Following the introduction of daily prednisolone/prednisone (PDN), a significant shift occurred, with around 85% of affected children achieving complete remission of proteinuria within 4–6 weeks, classifying them as having steroid-sensitive NS (SSNS). Despite this positive response, a substantial proportion (70–80%) of cases undergo at least one relapse during the follow-up period. Additionally, around 50% of cases experience frequent relapses or become steroid-dependent.[21] This historical context underscores the transformative impact of glucocorticoids on the prognosis and management of childhood NS. Prior research has indicated variations in the rates of outcomes in INS when categorized based on presentation characteristics such as gender, age, and ethnicity.[22,23]

CNS and INS are rare disorders and the sample size of 33 infants in this study allowed for a more in-depth exploration of the demographic and clinical characteristics, enhancing the generalizability of our findings. The meticulous documentation of clinical features and laboratory parameters further adds depth to the dataset, providing a comprehensive overview of the studied population. The single-center design may limit the generalizability of our findings to a broader population. We only noted short-term outcomes which warrants further studies exploring relatively long term outcomes in CNS and INS.

CONCLUSION

Infections were the most common associated conditions in congenital and infantile nephrotic syndrome. Short term outcomes exhibiting high mortality rates warrants early identification and treatment of congenital and infantile nephrotic syndrome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	Mashal Khan	COncept and Designing, Proof reading, Critical revisions.	
3	Bilqis Abroo	Concept and designing, Proof reading, Critical revisions.	
4	Uzma Shaikh	Data collection.	