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Hospitalization of Children with Nephrotic Syndrome

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Abstract

Background One of the most prevalent kidney disorders in children is nephrotic syndrome (NS). It is characterized by massive proteinuria, hypoalbuminemia, and edema.

Objective To study demographic and clinical characteristics of NS, hospitalization characteristics and the occurrence of complications during hospitalization, with comparison of some characteristics between hospitalized and non-hospitalized patients.

Methods Ninety NS patients, aged 1 to 15 years, who were either admitted to the Pediatric Ward of Al-Imamein Al-Kadhimein Medical City or followed in the Pediatric Nephrology Consultation Clinic between April 1, 2021, and May 31, 2022, were included in this prospective observational study. The main parameters studied were demographic and clinical characteristics of NS, complications during hospitalization, with comparison of some characteristics between hospitalized and non-hospitalized patients.

Results Male patients made up the majority (66.7%), of age group 5.1-10 years (44.4%), living in urban areas (70%), disease onset age of ≤5 years (66.7%), disease duration of >4 years (35.6%), and those with frequent relapses being the most prevalent kind (44.4%). Most patients stay in the hospital for 4-7 days (68.5%) and are admitted to the hospital an average of 45.6% of the time per year. The most prevalent complications were anasarca (76%), acute kidney injury (AKI) (17.8%), and scrotal edema (15.1%). Comparison between hospitalized and non-hospitalized children with NS, detected no significant difference according to age of patients, gender, age of onset, type of NS, residency and duration of disease.

Conclusion Complications of NS, especially serious ones during hospitalization, are not uncommon. High index of suspicion for complications, not to miss them.

Keywords nephrotic syndrome, hospitalization, children

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List of abbreviations: AKI = Acute kidney injury, INS = Idiopathic nephrotic syndrome, NS = Nephrotic syndrome, SRNS = Steroid-resistant nephrotic syndrome

Introduction

Nephrotic syndrome (NS) is one of the most prevalent kidney illnesses that affect children. It is typified by edema, hypoalbuminemia, and excessive proteinuria. In almost 95% of children with NS, edema is the initial symptom [(1)].

Patients with NS who fail to develop remission after 8 weeks of corticosteroid treatment are referred to as having steroid-resistant nephrotic syndrome (SRNS). These patients are at significantly higher risk for the development of complications of the disease and for the progression to chronic kidney disease (CKD) [(2)].

Among NS complications, infection is the most dangerous, approximately 60% of children with NS died from major infections that occurred before to the discovery of corticosteroids and antibiotics, which affected up to 75% of cases. Urinary tract infections (UTIs), sepsis, cellulitis, and peritonitis are the most frequent types of infections in people with NS. Pneumonia and meningitis are less common [3-5].

A small number of children have severe hypovolemia; this consequence is usually noted at the beginning or early stages of a recurrence. Hypovolemia might be brought on by diuretics, sepsis, or diarrhea [6].

One major and concerning clinical issue in NS patients is acute renal damage. Unfavorable consequences, such as death and persistent kidney failure [7].

Thromboembolism (TE) is a potentially life-threatening complication of NS. It has been observed that children with TE have an incidence ranging from 1.8 to 5%; children with SRNS had twice as high an incidence as children with SSNS [8].

The combination of acute lung injury (ALI) and renal failure results in a clinically significant 80% mortality rate. Acute kidney injury (AKI) is the cause of increases in circulating chemokines, cytokines, and activated innate immune cells. These elements start a pathogenic cascade that eventually results in ALI and acute respiratory distress syndrome (ARDS) through the water imbalance [9].

Fluid from pulmonary edema has many plasma proteins, including proteolytic enzymes, proteins, fibrinogen, and fibrin, in its contents, which can lead to the destruction of the surfactant proteins [10]. Studies have estimated the prevalence of hypertension in different patient populations with NS to range from 8 to 59.1% [11].

Admitting all patients with new-onset NS to the hospital is not necessary. Possible medical indications for admission include the following: anasarca, especially when resistant to outpatient therapy or accompanied by respiratory compromise, massive ascites, or scrotal edema, significant hypertension, anuria or severe oliguria, and significant azotemia.

About 17% of hospitalizations for NS are associated with an infection; the most common infections are bacteremia, pneumonia, peritonitis, cellulitis, and urinary tract infections. About 8% of patients had an admission because of AKI, and 1% have TE [12,13].

This study aimed to study the demographic and clinical characteristics of children with NS. Also, to study the hospitalization characteristics in the last year and the complications of those children during hospitalization. Additionally, to compare some characteristics between hospitalized and non-hospitalized children.

Methods

A prospective study was performed on 90 children ages 1-15 with NS managed at the Pediatric Nephrology Consultation Clinic or admitted to the Pediatric Ward in Al-Imamein Al-Kadimein Medical City and Central Child Teaching Hospital. From April 1st, 2021 until May 31st, 2022, the study is conducted. Massive proteinuria and hypoalbuminemia, which lead to hyperlipidemia and edema, are characteristics of idiopathic NS [14].

The study excluded patients with secondary NS and NS <1 year of age at onset.

Relapsed NS is defined as proteinuria >40 mg/h/m^2 or >50 mg/kg/day or Albustix +++ for 3 consecutive days after having been in remission. Frequent relapses (FR) are 2 or more relapses within 6 months of the initial response or 4 or more relapses within a period of 1 year, while infrequent relapses (IR) are less than 2 within 6 months or less than 4 for any year thereafter. Steroid-responsive NS is complete remission achieved with steroid therapy. Steroid-resistant NS is failure to achieve remission following 4-week prednisone 60 mg/m^2 ± followed by three methylprednisolone pulses [14,15].

A questionnaire designed by the researchers included: 1) Demographic data: age, sex, residency. 2) Clinical data: age of diagnosis of NS, type of NS. 3) Hospitalization statistics

comprised the quantity of patients admitted in the previous year, the duration of hospital stay, and the difficulties that necessitated hospitalization. It was determined that peritonitis, with or without culture confirmation, constituted a significant complication. AKI is characterized by an increase in serum creatinine by >0.3 mg/dl within 48 hr or to >1.5 times baseline, which is known or presumed to have occurred within the past seven days, or urine volume <0.5 ml/kg/hr for 6 hr [7].

Hypertension is defined by systolic or diastolic blood pressure >95th centile for gender, age, and height [16].

Pneumonia, viral or bacterial, presents as fever, shortness of breath, and agitation. Pleural effusion (radiologically confirmed). Serious edema, which includes scrotal or anasarca (when edema is massive and generalized) [17].

Statistical analysis

Data were analyzed and presented using the statistical package for social sciences (SPSS) version 23 and Microsoft Office Excel 2019. Qualitative (categorical) variables were expressed as numbers and percentages. Quantitative (continuous) variables were expressed as the mean and standard deviation. The level of significance was considered to be a P-value less than 0.05.

Results

Table 1 displays the demographics of NS patients, indicating that there were more males than females, that the most prevalent age group was 5.1-10 years, and that urban rather than rural populations were more affected.

Table 1. Demographic characteristics of children with nephrotic syndrome

Characteristic		N=90	%
Sex	Female	30	33.3
	Male	60	66.7
Age groups (yr)	≤5	21	23.3
	5.1-10	40	44.5
	>10	29	32.2
Residency	Rural	27	30.0
	Urban	63	70.0

Age mean±SD = 8.19+3.47 yr, Range 0.92-15 yr

Table 2 displays the disease characteristics in NS patients. It shows that the most common age of onset was between 1 and 5 years, and most patients had been sick for at least 4 years. When it came to the type of NS, FR (n = 40, 44.4% of patients), followed by IR (n = 34, 37.8%), and finally SRNS (n = 16, 17.8% of patients).

As shown in Table 3, the total number of hospitalizations is 123 among 73 patients, while 17 children (18.9%) had no hospitalizations in the last year. Most frequently, 41 patients (45.6%) had 1 hospitalization per year, then 2 admissions. On the other hand, only 4 and >4 admissions per year were recorded for 1 patient (1.1%) and 2 patients (2.2%), respectively.

Table 4 illustrates that the majority of patients stay in the hospital for four to seven days, followed by sixteen patients (21.9%) who stay for more than seven days, and just seven patients (9.6%) who stay for one to three days. Based on data from 73 hospitalized patients, table 5 indicates that 59 patients (76%),

followed by AKI in 13 patients (17.8%), and 11 patients (15.1%) had scrotal/vulvar edema, which were the most prevalent sequel. No female patient experienced vulvar edema; all patients were male. Eight patients (11.0%) had pneumonia, six patients (8.2%) had peritonitis, three patients (4.1%) had pleural effusion and hypertension, and one patient (1.4%) had appendicitis.

Table 2. Disease characteristics of children with nephrotic syndrome

Characteristic		N	%
Age of onset of nephrotic syndrome (yr)	≤5	60	66.7
	5.1-10	26	28.9
	>10	4	4.4
Duration of the disease (yr)	1	18	20.0
	2	15	16.7
	3	12	13.3
	4	13	14.4
	>4	32	35.6
Type of nephrotic syndrome	FR	40	44.4
	IR	34	37.8
	SRNS	16	17.8

Table 3. Distribution of patients according to the number of hospitalizations in the last year

Parameter		N	%
Number of hospitalizations	Nil	17	18.9
	1	41	45.6
	2	19	21.1
	3	10	11.1
	4	1	1.1
	>4	2	2.2

Table 4. Distribution of 73 patients according to length of stay in the hospital

Parameter		N	%
Length of stay in hospital (day)	1-3	7	9.6
	4-7	50	68.5
	>7	16	21.9

Hospital stay mean ±SD = 5.07±3.35 day

Table 5. Distribution of 73 patients according to complications during hospitalization

Complication	N	%
Anasarca	59	76
AKI	13	17.8
Scrotal/vulvar edema	11	15.1
Peritonitis	8	11.0
Pneumonia	6	8.2
Hypertension	3	4.1
Pleural effusion	3	4.1
Appendicitis	1	1.4
Convulsion	0	0

Note: The patient may have more than one complication

A comparison of some characteristics between hospitalized patients (n = 73) and non-hospitalized patients (n = 17) is presented in table 6. Hospitalization was not statistically correlated with any of the following characteristics: NS type, residency, age of onset, patient sex, length of NS, or any of these factors.

Table 6. Comparison of some characteristics between hospitalized and non-hospitalized children with NS

Characteristic		Without Hosp. N=17, No. (%)	With Hosp. N=73, No. (%)	P value
Sex	Female	7 (41.2)	23 (31.5)	0.569*
	Male	10 (58.8)	50 (68.5)	
Age groups (yr)	≤5	2 (11.8)	19 (26.0)	0.261**
	5.1-10	7 (41.2)	33 (45.2)	
	>10	8 (47.1)	21 (28.8)	
Age of onset of NS (yr)	≤5	9 (52.9)	51 (69.9)	0.507***
	5.1-10	6 (35.3)	20 (27.4)	
	>10	2 (11.8)	2 (2.7)	
Types of NS	FR	4 (23.5)	36 (49.3)	0.126**
	IR	8 (47.1)	26 (35.6)	
	SRNS	5 (29.4)	11 (15.1)	
Residency	Rural	5 (29.4)	22 (30.1)	1.000*
	Urban	12 (70.6)	51 (69.9)	
Duration of the disease (yr)	1	4 (23.5)	14 (19.2)	0.580***
	2	4 (23.5)	11 (15.1)	
	3	1 (5.9)	11 (15.1)	
	4	0 (0.0)	13 (17.8)	
	>4	8 (47.1)	24 (32.9)	

* P value by Fisher exact test, ** p value by chi square test, p value by Yates chi square test

Discussion

The present study supports previous published reports that demonstrate male predominance in children with NS [14,16,18-20].

The majority of patients in this study were in the age group of 5.1-10 years, which is similar to the Ethiopian study [20]. Other studies showed the age of patients with NS ≤5 years was the commonest [21,22]. The primary reason for this discrepancy is that the majority of the study's patients had prior diagnoses before being sent to this tertiary facility.

In this study, most patients lived in urban areas due to the geographical location of this hospital and its peripheries, which agrees with several studies [19,22-24].

The age of onset of the disease was ≤5 years, which agrees with several other studies [19,25-27]. The difference between age of onset and age at presentation was evident here, which reflects the late referral of patients to this hospital.

Due to consistent, routine hospital and consultant clinic visits as well as their dedication to their treatment, the majority of patients (35.6%) have had their diseases for longer than four years. Based on various research with slightly different percentages, it is evident that FR is the predominant kind of NS [1,22,25,28].

Only 2 patients (2.2%) had more than four hospital admissions, compared to 45.6% of patients who were admitted more frequently than once annually. This could be explained by the fact that even though the majority of patients experienced FR, our patients were able to manage their mild-to-moderate relapses without the need for hospitalization. This was in line with the findings of the Wang et al. study, which showed that 71% of the patients had a yearly hospital stay [29].

In the Wang et al. study, the length of stay in the hospital was approximately 4 days due to less serious complications, whereas the majority of patients had a stay of 4-7 days, which indicates the presence of serious complications that require more hospital days and multiple therapies [29].

Carpenter et al. looked at children who were hospitalized for two years with both NS and infection. They found that the usual number of hospitalizations was two, and the typical length of stay was ten days. This demonstrates how different hospitalization reasons will affect the number of days spent in the hospital [30].

In 76% of instances, anasarca and widespread edema were the most frequent sequel. Severe hypoproteinemia and extensive proteinuria led to edema. Because he considered generalized edema to be a presentation rather than a consequence, generalized edema impaired 100% of the subjects in the Albar et al. trial [21]. In the Kumar et al. study, 81 out of 199 NS patients had an admission recommendation for anasarca [26].

AKI accounted for 17.8% of the overall complications during hospitalization in this study, making it the second most prevalent complication. While earlier research indicated that the frequency of AKI in children with idiopathic NS (INS) was less than 10%, a new publication puts the rate as high as 58.6%. This suggests that the incidence of AKI in children with INS may be rising. This might be because more people are using medications like tacrolimus and cyclosporine, particularly those who are steroid-resistant. Additionally, in children hospitalized with NS, the use of nephrotoxic antibiotics and diuretics such as furosemide has been linked to the development of AKI. A higher frequency of AKI may also result from a lower diagnostic threshold for serum creatinine than in years past, when reports of acute renal failure were the primary cause for concern [32]. Recent research on hospitalized children with NS found that methylprednisolone pulse treatment, a lower albumin level, and longer disease duration were risk factors for AKI [33]. Wide range of AKI was found in different studies as 16.2-58.6% (20,33-35).

Vulvar or scrotal edema was the third most frequent hospitalization-related consequence. Patients diagnosed with NS frequently have scrotal involvement; this is typically limited to swelling that can be so unpleasant as to interfere with daily activities. Furthermore, in cases of severe edema, it may be complicated by significant infections and tears in the scrotal wall. Extended periods of edema may also

result in fibrotic alterations [36]. Higher figures for scrotal edema came from an Egyptian study in 2022 and an Indian study in 2012, at 50% and 37.3%, respectively. Those studies took scrotal edema as part of generalized edema as the presenting sign [37,38].

Peritonitis occurred in 11% of all patients and was the most common infection in patients with NS. Two studies detected peritonitis with 24% and 26.1% respectively (26,34), while lower rate detected by 3 studies 3.9-8.3% ([30,39,40]. Different rates are due to inclusion criteria of hospitalized patients whether with infection only or not

A low serum albumin level, ascites, and protein and immunoglobulin losses in the urine can all lead to peritonitis. Usage of immunosuppressive drugs, encapsulated gram-positive bacteria, especially Streptococcus pneumoniae, are the main cause of peritonitis, however gram-negative organisms can also be the culprit [27,39].

Pneumonia occurred in 8.2% of patients as a result of complications during hospitalization. Two studies reported lower results [30,40]. While higher results came from 3 others (18%, 14.3%, 41.7%) [26,34,39]. The higher findings can be attributed to the increased sample size and the discussion of pneumonia as a component of the infection. Less immunity from long-term steroid usage and sporadic vaccinations led to pneumonia. It may also be a reflection of the overall increased prevalence of respiratory infection in the community over the last 30 years and prolonged stay in the hospital, or due to mechanical pressure on the lung due to massive ascites and pleural effusion leading to stasis of lung fluid [39].

Hypertension occurred in 4.1% of the participants in this study; other studies, such as Samanta et al. [41], showed hypertension in 36.4% of SSNS children only, while Imbusi et al. 49.2%, as well as Manasa et al. 54% [20,42]. Both of these studies discussed hypertension in NS as a whole, including SRNS, which has a higher rate of HT. Various factors contribute to elevated BP in patients with NS, such as intense vasoconstriction, hyperlipidemia, side effects of multiple courses of daily steroid and prolonged maintenance therapy, and changes in glomerular filtration dynamics due to the disease process itself, like activation of the renin-angiotensin-aldosterone system [11].

El-Halaby et al. showed pleural effusion occurred in 8.3% compared to 4.1% in this study [37]. The occurrence of pleural effusion may be due to massive hypoproteinemia that leads to a decrease in oncotic pressure that tends to be bilateral with a predilaction for the subpulmonic space [31,36].

From the comparison between hospitalized and non-hospitalized patients as shown in table 6, this study did not conclude a statistical difference between both groups in the studied parameters: sex, age, age of onset, type of NS, residency, and duration of the disease. Previous study detected the dominance of FR with statistical significance, and this may be due to the difference in sample size [29].

Complications of NS, especially serious ones during hospitalization, are not uncommon and need a proper management. Outpatient management of some complications needs special research to be done.

In conclusion, the majority of patients were hospitalized once per year for 4-7 days, the most common complications among patients with NS were anasarca, AKI, and scrotal edema. There were no discernible differences in age, gender, age of onset, type of NS, residency, or length of disease between children with NS who were hospitalized and those who were not. High index of suspicion to make sure complications including pneumonia, peritonitis, and scrotal edema are not overlooked. Appropriate and comprehensive investigations are necessary to detect and treat AKI at an early stage.

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Author contribution

All authors have participated sufficiently in the intellectual content, conception and design of this work or the analysis and interpretation of the data, as well as the writing of the manuscript.

Conflict of interest

There is no conflict of interest.

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