Childhood nephrotic syndrome in Southeast Nigeria: The old story or any change in pattern?

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ABSTRACT

Background: The chronic course of nephrotic syndrome (NS), it is racial/regional variations, and associated risk of end-stage renal disease is of great pediatric importance. This underscores the need to study the characteristics of this cohort of patients in every nephrology setting. **Objective:** This study was aimed at documenting the characteristics of children presenting with NS in our hospital. **Materials and Methods:** This was a cross-sectional descriptive study of children aged 29 days–16 years admitted and managed for NS over 5 years at the Pediatric Nephrology Unit of the Abia State University Teaching Hospital, Nigeria. Children diagnosed with NS in our setting were consecutively enrolled in the study. The parameters documented and analyzed for each patient with NS included Biodata, presenting complaints, duration of illness before the presentation, intake of herbal concoctions, results of investigations done, response to the steroids, duration of treatment before remission, and outcome of admission. Steroid sensitive NS was followed up for a median (range) period of 18.2 (12.0–24.0) months to monitor remission and relapse. **Results:** A total of 6108 children were admitted into the pediatric wards during the study period, of which 104 were renal disorders. NS accounted for 0.8% of all the pediatric admissions and 49 (47.1%) of the admitted renal disorders. Male:female ratio was 2.3:1. The mean age was 8.35±3.99 years, with peak ages between 7 and 9 years. The major clinical features at first presentation were pedal edema (93.9%) and oliguria (87.8%). A total of 19 patients (38.9%) took herbal concoctions before the presentation ($p<0.05$) and 12 patients had culture-proven urinary tract infections. There were four patients seropositive to human immunodeficiency virus and two had sickle cell anemia. There were 39 patients (90.7%) who were steroid-sensitive, while four (9.3%) were steroid-resistant. A total of 47 patients were discharged. There was one patient who was referred, while one signed against medical advice. Over this period, 76.9% remained in remission, while relapse was noted in 23.1% of patients. The mortality was 2.0%. **Conclusion:** NS forms a significant part of our pediatric admissions. Herbal concoction intake among our cohort with NS was high. There was an increased response to the steroid, even in older children. A majority maintained their remission while on follow-up. The mortality rate was low. The prognosis of NS in African children is changing for the better, age notwithstanding.

Key words: *Aba, Children, Nephrotic syndrome, Nigeria*

Nephrotic syndrome (NS) is a chronic kidney disease characterized by heavy proteinuria, hypoalbuminemia, massive edema, and hyperlipidemia [1,2]. It is the most common chronic glomerular disease of children globally, with associated significant morbidity and mortality [3]. Worldwide, it has an estimated annual incidence of 1–7 cases/100,000 children/year, with a cumulative prevalence of 16/100,000 children [4-6]. In tropical Africa, the overall incidence of NS was estimated at 0.23–1.34% of hospital admissions [7].

The epidemiology, clinical characteristics, response to therapy, and outcome of NS vary by ethnicity and region [8]. These variations could be due to various reasons, including race, availability, and accessibility of health care resources. Different studies from various centers in Nigeria have exhibited specific demographic and clinical patterns of the disease [9-13]. The knowledge of the pattern of presentation and course of a childhood disease will help the pediatrician and hospital stakeholders in future health policy formulation, resource allocation, and optimal management protocols for such patients.

To date, no study has been done on this cohort of children with NS presenting to the Pediatric Nephrology Unit of our health facility. This study was therefore aimed at documenting the prevalence of NS among our admitted pediatric patients, their clinical characteristics at initial presentation, response to steroid, outcome of admission, presence of relapse for those that entered into remission, and final outcome at the end of the follow-up period.

MATERIALS AND METHODS

This was a cross-sectional descriptive study of children aged 29 days–16 years admitted and managed for NS over 5 years

(October 2013–2018) at the Pediatric Nephrology Unit of the Abia State University Teaching Hospital, Nigeria. NS was defined as a clinical syndrome with 24-h urine protein >40 mg/m^2/h or spot urine protein: Creatinine ratio >200 mg/mmol, hypoalbuminemia (serum albumin <25 g/L), generalized edema, and hypercholesterolemia (serum cholesterol >5.2 mmol/L) [3]. The exclusion criteria were children aged <29 days or >16 years, with malignancies and children who were already on steroids or immunosuppressive drugs before the presentation. Ethical clearance was obtained from the ethics committee of ABSUTH, Aba, before commencing on the study.

After the diagnosis of NS was confirmed, patients were started on prednisolone at 60 mg/m^2/day or 2 mg/kg/day, as daily morning dose for 6–8 weeks by Kidney Disease Improving Global Outcomes (KDIGO) recommendations [14,15], except where steroid was contraindicated. The steroid response was determined by the occurrence of remission. Those that achieved remission were termed steroid-sensitive NS (SSNS), while the others were termed steroid-resistant NS (SRNS). Following remission, the dose was reduced to 40 mg/m^2 on alternate days for 4 weeks and gradually tapered over 3–5 months. Steroid dependence (SD) was treated with the addition of levamisole (2.5 mg/kg/day) on an alternate day basis. Cyclophosphamide (oral or intravenous) was used for patients with severe SD not responding to alternate day levamisole. Steroid resistance was treated with oral (2 mg/kg/day for 8 weeks) or intravenous (500 mg/m^2/month for 6 months) cyclophosphamide, and angiotensin-converting enzyme inhibitors (either enalapril or lisinopril). The SSNS patients were followed-up for a median (range) period of 18.2 (12.0–24.0) months to monitor their disease remission status, and document relapse, if any.

Parameters documented and analyzed for each patient with NS included age, sex, presenting complaints, duration of illness before the presentation, intake of herbal concoctions, presence of hypertension (high blood pressure [HBP]), results for: Urinalysis, microscopic hematuria, urine microscopy/ culture/sensitivity, serum electrolytes/ urea/creatinine, screening for hepatitis B and C infections, blood film for malaria parasite, hemoglobin genotype, and human immunodeficiency virus (HIV) screen. The response to steroids, the duration of treatment before remission, rate of relapse, and outcome of illness were also documented.

The data were analyzed using SPSS software, version 24.0. The frequency tables were generated for all major variables of interest. Chi-square test was used to test for the significance of the association between NS and other variables. A confidence interval of 95% was used, and for all analyses, $p<0.05$ was taken as statistically significant.

RESULTS

A total of 104 renal disorder patients were admitted during the study period. NS accounted for 47.1% of these admissions. Male:female ratio was 2.3:1 (Table 1). The mean age was 8.35±3.99 years, with peak ages between 7 and 9 years. The age range was 5 months–16 years (Table 1). The majority (80%) of the patients presented to the hospital >7 days after onset of illness (Table 1). A significant percentage (34.7%) presented as late as more than a month after onset of illness (Table 1).

Table 2 shows that the major clinical features were pedal edema 46 (93.9%) and oliguria 43 (87.8%) at initial presentation to the hospital, before steroid trial. A total of 19 (38.9%) patients took herbal concoction ($p<0.05$) before coming to the hospital. There was no gross hematuria. Thirty-seven patients had at least one plus of malaria parasite in their peripheral blood film, all of which were *Plasmodium falciparum*. A total of 12 patients (24.5%) had culture-proven urinary tract infection (UTI). All were seronegative to hepatitis B and C. The serum electrolyte, urea, and creatinine results were normal for all at presentation. However, one patient with HIV-associated nephropathy (HIVAN) developed acute kidney injury while on follow-up.

A total of 47 (95.9%) of the total number of patients were discharged and followed up. Only 43 patients were given the steroid therapy because the later was contraindicated in sickle cell nephropathy and HIVAN. There were 39 patients (90.7%) who were SS, while four (9.3%) were SR. The median (range) duration of responsiveness to steroid was 21 (7–50) days, for the SSNS. The 39 SSNS patients were followed-up for a median (range) period of 18.2 (12.0–24.0) months to monitor their

Table 1: Demographic profile of the study population

Demographic profile	Number (%)
Age (Years)	
<5	10 (20.4)
5–10	24 (49.0)
11–16	15 (30.6)
Sex	
Male	34 (69.4)
Female	15 (30.6)
Duration of illness (days)	
<7	6 (12.2)
7–14	20 (20.4)
15–30	16 (32.7)
>30	17 (34.7)
Total	49 (100.0)

Table 2: Clinical parameters of the study population at the first presentation to the hospital

Parameters	Number (n=49) (%)
Herbal concoction	19 (38.9)
Leg swelling	46 (93.9)
Oliguria	43 (87.8)
Generalized body swelling	38 (77.6)
Dysuria	17 (34.7)
Microscopic hematuria	21 (42.9)
Hypertension	5 (10.2)
Positive malaria parasite	37 (75.5)
Positive HIV screen	4 (8.2)
SS genotype	2 (4.1)

disease remission status. Over this follow-up period, 30 (76.9%) remained in remission, while nine (23.1%) relapsed. There were five (12.8%) patients who relapsed frequently, while four (10.3%) had infrequent relapses. There were two (5.1%) who were steroid-dependent.

There was no death recorded among the admitted patients, but one of the steroid-dependent patients, who became non-compliant with medications, died during follow-up. This gave a mortality rate of 2.0%. There were two SRNS patients who, on follow-up, eventually achieved remission on intravenous cyclophosphamide, 500 mg/m^2 monthly for 6 months, given in combination with low dose alternate-day prednisolone. The other two were lost to follow-up. The two HIVAN patients that were followed up remained stable on highly active retroviral therapy, while the two patients with sickle cell anemia (SCA) were eventually lost to follow up.

DISCUSSION

NS accounted for 0.8% of all the pediatric cases admitted over the study period. This is higher than the 0.23% reported by Ibadin *et al*. [10] but lower than the 1.34% reported by Okoro *et al*. [12], both in Nigeria. NS also accounted for a significant percentage (47.1%) of all the renal disorders seen within the study period, which buttresses the fact that it is the most common chronic glomerular disease in children [16,17].

The male preponderance of NS in our center was in agreement with the previous studies in and outside Nigeria [1,4,10-12,18]. The peak age of 7–9 years observed in this study was in accordance with the findings by Okoro *et al*. [10], Obiagwu *et al*. [11], Adedoyin *et al*. [18], and Adeleke *et al*. [19]. Kumar *et al*. [20], and Ehrich *et al*. [21] also documented a peak age of 7–9 years among their study population. In contrast, Okoro *et al*. [12], Anochie *et al*. [22], and Abbas *et al*. [23] recorded lower peak ages (<5 years) from their studies. The higher peak age of about 12 years was documented by Abbas *et al*. [23] and Doe *et al*. [24]. These peak age variations may be due to environmental, geographical, or racial factors.

Edema of various degrees and oliguria was the common presentation by our cohort. Varying degrees of edema has remained the most frequent presentation by this cohort of children in most studies [4,12,13,22,25]. The oliguria and massive edema of NS, unlike other symptoms of the disease, are worrisome and may provoke parents to seek medical attention more readily. Greater than 50% of our patients presented to the hospital after 2 weeks of the onset of illness. This reflects the prolonged period that patients use in self-medication and ingestion of herbal drugs to achieve a cure before coming to the hospital.

A significant number (38.9%) of our patients took some form of the herbal concoction before the presentation. This is higher than the 27.3% documented in an earlier study by Okoronkwo *et al*. [4]. The use of herbal drugs as complementary or alternative medication for various illnesses is said to be rising in our environment [26]. Although the intake of herbal concoction was significantly associated with NS in this study, we cannot categorically substantiate its causative effect on NS as the patients already had symptoms of illness before their use of herbal preparations. We also noted that all the four patients who were SR took herbal concoction before coming to the hospital. However, the extent to which it affected their response to steroids is beyond the scope of this study.

The prevalence of HBP (10.2%) in our study was lower than the 22.7%, 34.8%, 35.0%, 43%, and 41.4% reported by Okoronkwo *et al*. [4], Anigilaje *et al*. [26], Obiagwu *et al*. [11], Ladapo *et al*. [13], and Ibadin *et al*. [10], respectively. The prevalence of microscopic hematuria in the index study was comparable to the 44%, and 41.2% in Lagos [13] and Abuja [25], respectively, but lower than the 60% and 80.0% in Benin [10] and Kano [11]. The higher prevalence of HBP and microscopic hematuria documented in some of the aforementioned studies may parallel the non-minimal change histological patterns recorded in those studies.

SS among our patients was high. This compares well with some previous studies within and outside Nigeria [6,10,13,22,25,27,28]. Of note is that majority of these comparable studies had a cohort of patients with peak ages of <5 years, except the study by Anigilaje *et al*. [25]. A previous study on NS [4] recorded a high rate of SR among their study population. This was attributed to the higher ages of the children that presented with NS in that center. The high SS (90.7%) in this study and the 73.9% from Abuja, among a cohort with mean peak ages of approximately 8 years, may predict a changing pattern of steroid responsiveness in older black children with NS. This is contrary to previous studies [11,13,18] that recorded high SR among older children.

Again, the high prevalence (87.7%) of idiopathic NS in this study may have positively impacted the response to the steroid. Secondary NS (SNS) was noted in only six patients (four with HIVAN and two with SCA). This low prevalence of SNS is comparable to studies by Ladapo *et al*. [13], Anigilaje *et al*. [25], and Olowu *et al*. [29], where a reduction in the incidence of infectious diseases, as a secondary cause of NS in African children, has been suggested.

A total of 30 (76.9%) of our SSNS patients remained in remission till end of the follow-up period, while 23.1% relapsed. Those that relapsed were higher than the 16.7% in Abuja [25], Nigeria, but far lower than the 93.8% reported by Anochie *et al*. [22], 56.3% in Ghana [24], and 45% in Saudi Arabia [30]. Esezorbor *et al*. [7] noted that half and two-thirds of their SSNS relapsed during their 1st and 2nd years of follow-up, respectively.

Environmental, regional, and geographical variations may also affect the rate of steroid relapse or dependence among children from different localities. However, more importantly, the longer course (8 weeks) of steroid and larger cumulative doses we used in our study may have positively impacted the maintenance of remission among our cohorts. Most of the older studies [22,24,30] with higher relapse rates used a shorter duration of daily prednisolone (4–6 weeks) before the KDIGO recommendations of 8 weeks since 2012 [31].

The rate of UTI among our cohort is comparable to the 25% reported in Lagos [13]. It is, however, higher than the 4.3% in

Abuja [25] but lower than the 44.8% in Benin [10]. All the UTIs in our study as well as those in Abuja were caused by *Escherichia coli*, while *Staphylococcus aureus* was a major uropathogen in Benin. UTI has been noted as a common complication in patients with NS [10,32].

The index mortality rate was much lower than documented in a nearby center in the same state of study [4]. This can be explained by the increased rate of SRNS in the older study [4]. SRNS is known to be associated with higher mortality [25].

Compared to other Nigerian studies, the index mortality rate, though lower, agreed with previous findings of 6.9% [10], 6.5% [13], and 8.7% [25] where mortality rates were <10% among highly SS patients with NS.

We faced some limitations in the index study. Only one of our SRNS case was biopsied. The other three patients rejected renal biopsy. This affected our comparison with other studies where all or most of their patients were biopsied. The small sample size in this study is another major limitation. Some investigations such as complements (C3 and C4) assays, antinuclear antibody tests, and anti-neutrophil cytoplasm antibody tests are not currently done in our center. These may have helped our records on etiology. Moreover, our cohort had a short median follow-up period of 18.2 months and we are mindful of the limitation in interpreting steroid relapse and dependence in view of this time frame.

CONCLUSION

The prevalence of NS was 47.1% among the renal disorders seen over the study period. Herbal concoction intake among our cohort with NS was high. There was an increased sensitivity to steroids even in older children, with the majority maintaining their remission while on follow-up. The mortality rate and rate of relapse after remission were low. The prognosis of NS in African children seems to be changing for the better, age notwithstanding.

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