ORIGINAL ARTICLE

Childhood nephrotic syndrome at the University of Abuja Teaching Hospital, Abuja, Nigeria: a preliminary report supports high steroid responsiveness

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ABSTRACT

The response to steroid in childhood nephrotic syndrome (CNS) varies across geographical regions, depending on aetiology, genetics, and the underlying pathology. Recently, there is an increasing steroid responsiveness among Nigerian children with nephrotic syndrome (NS). This is the first report of CNS at the University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria, between 15th January 2016 and 30th June 2018. Prednisolone was administered to all the children with NS according to the regimen of the International Study of Kidney Disease in Children. There were 46 children aged 17 months to 18 years, including 37 males and 9 females. The peak age was 6–10 years with a mean age of 8.2 ± 4.4 years. Forty-one (89.1%) had idiopathic NS (INS). Secondary NS occurred in five (10.9%) children with hepatitis B infection, sickle cell anaemia, haemolytic-uraemic syndrome, and post-infectious glomerulonephritis (two cases). *Plasmodium malariae* was not seen. Overall, steroid-sensitive NS (SSNS) was seen in 34 (73.9%) and in 32 (78%) with INS. Five (16.7%) of the 30 with SSNS relapsed on follow-up. Twelve (26.1%) were resistant to steroid (steroid-resistant NS, SRNS). Renal biopsies in five SRNS revealed focal segmental glomerulosclerosis in three, minimal change lesion in one, and severe interstitial fibrosis/glomerulosclerosis in another one. Four (8.7%) children who had SRNS died. A child with SRNS is surviving on renal transplant from a living-unrelated donor. The study supports the notion that steroid responsiveness is increasing among ethnic black Nigerian children. Pre-treatment renal biopsy may be unwarranted.

KEYWORDS

Childhood nephrotic syndrome, Steroid responsiveness, Abuja; Nigeria.

INTRODUCTION

Nephrotic syndrome (NS) is a manifestation of pathological changes in the kidney that culminates in the inability of the glomerulus to disallow the loss of a large quantity of protein in the urine [1–3].

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The consequent heavy proteinuria is accompanied by hypoalbuminaemia, hyperlipidaemia and a varying degree of oedema [1–3]. Children with NS can present with acute life-threatening conditions like hypovolaemia, acute kidney injury (AKI), hypercoagulation and infection [4,5]. NS can also progress to end-stage kidney disease (ESKD) when it does not respond to the steroid [6].

The annual incidence of NS in the United States and Europe is estimated at 7/100,000 [7], but the overall incidence of NS is difficult to estimate in Africa [8]. This is because most African countries are plagued with many challenges, including a dearth of paediatric nephrologists, lack of electron and immunofluorescent microscopes, a lack of capacity to do renal biopsies and/or interpret histopathology findings and unavailability of therapeutic medications. In addition, the absence of national renal registries and large-scale epidemiological and randomised controlled studies also make the report on the incidence of NS difficult [8]. Cumulatively, these challenges make NS be un-diagnosed, under-diagnosed and under-reported. In actual fact, among the 54 sub-Saharan African countries, only 17 have information on the burden of childhood NS [9].

Childhood NS (CNS) is heterogeneous and the incidence and clinical presentations vary across geographic regions, depending on genetics and environmental influences [10–12]. In Europe and North America, about 90% of CNS are idiopathic. In addition, minimal change disease (MCD) accounts for 85% of the cases with steroid responsiveness seen in more than 90% of the MCD [7,13–15].

However, in blacks, CNS is characterised by patterns that include older age at onset, the paucity of MCD, steroid resistance in a majority, identifiable causes in many, with most children progressing inevitably to ESKD [16–19]. For example, steroid resistance is at between 35% and 92% for CNS in Nigeria [20–29], a finding that also reflects the underlying histopathology which reveals a rarity of MCD but a varying burden of membranoproliferative glomerulonephritis (MPGN), focal mesangial proliferative lesion and focal segmental glomerulosclerosis [20–29].

In Nigeria, although the earlier experiences with steroid therapy among children with NS appear not to be favourable [20–29], recent studies from several regions in Nigeria have begun to document high and increasing rates of steroid responsiveness [9,19,30]. Unfortunately, there is still a dearth of information on clinical characteristics, the natural history and steroid responsiveness of NS among Nigerian children.

Thus, the aim of this study is to report the socio-demographic, the clinical presentations and the therapeutic response to steroid among children (aged 1–18 years) with NS at the University of Abuja Teaching Hospital (UATH), Abuja, North Central, Nigeria, from 15th January 2016 till 30th June 2018. This study is unique as it is the first to describe the epidemiology of NS among Nigerian children in Abuja, the cosmopolitan Capital city of Nigeria.

MATERIALS AND METHODS

Study area

This descriptive cross-sectional study was conducted at the Nephrology Unit of the Department of Paediatrics, UATH, Abuja, Nigeria. The UATH is a 350 bed tertiary health hospital located in Gwagwalada Area Council, Abuja, North Central Nigeria. Abuja is a planned city that was built mainly in the 1980s [31] becoming the country's capital city in 12th December 1991 [32]. The indigenous inhabitants of Abuja are the Gbagyis, the Bassas, the Gwandaras, the Gedes, the Ganaganas and the Koros; however, the three major Nigerian tribes of Hausa, Yoruba and Igbo also reside in the city in large numbers.

Data abstraction

Data of participants aged between 1 and 18 years who presented with NS between 15th January 2016 and 30th June 2018 were included in the study. By 15th January 2016, the Nephrology Unit had developed an electronic data capturing system (on Microsoft Excel Worksheet) for collecting data on children with NS. The information abstracted from this system included socio-demographic data and the clinical presentations of the NS. Other data were the investigations' results of the spot urine protein/creatinine ratio, urinalysis, plasma albumin and protein, fasting serum

triglyceride/cholesterol levels, anti-streptolysin O titre, serum complements C3/C4, urine sediment microscopy, urine culture, serum electrolytes, urea and creatinine, *Plasmodium malariae* and *Plasmodium falciparum* parasites, full blood count, haemoglobin genotype, hepatitis B, hepatitis C, human immunodeficiency virus and renal ultrasound scans. Glomerular filtration rate (GFR) was also estimated from serum creatinine by Schwartz formula for each patient. The time to remission of proteinuria in days following the commencement of steroid was noted for each subject coming with the first diagnosis of NS.

Definitions

The following definitions apply to the management of the NS in this study:

NS is defined as the presence of oedema, massive proteinuria of spot urine protein creatinine ratio ≥ 200 mg/mmol, hypoalbuminaemia (serum albumin ≤25 g/l) and hypercholesterolemia (serum cholesterol > 5.2 mmol/l) [1,33,34]. However, "although the classic definition of nephrotic syndrome includes (1) nephrotic-range proteinuria, (2) hypoalbuminemia, (3) oedema and (4) hyperlipidemia, only the first criterion is essential for diagnosis, especially in clinical trials, because oedema, hypoalbuminemia, and hyperlipidemia are not present in all cases of idiopathic nephrotic syndrome" [35].

Secondary NS (SNS) refers to proven aetiology extrinsic to the kidney [3,33]. Thus, SNS include (1) autoimmune and vasculitic diseases, such as Henoch–Schonlein purpura, systemic lupus erythematosus and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; (2) infectious diseases, such as congenital syphilis, malaria, human immunodeficiency virus (HIV), and hepatitis B and C; (3) malignancy; (4) environmental and drug exposure, such as heroin and mercury and (5) systemic diseases such as diabetes mellitus, among many other causes [3,33].

Idiopathic NS (INS) is when NS is not congenital, infantile or secondary [3,33].

Atypical NS is when children with NS present with certain features at presentation, including age less than 12 months or greater than 12 years, persistent hypertension, impaired renal function, gross haematuria, low plasma C3 and viral hepatitis B or C [33].

Complete remission/steroid responsiveness is when urine dipstick albumin becomes negative or trace for 3 consecutive days [34].

Partial remission (PR) is proteinuria level of 1+/2+ proteinuria by dipstick for 3 consecutive days [34].

Initial or earlier responder (steroid sensitive NS-SSNS): An attainment of complete remission within the initial 4 weeks of corticosteroid therapy as defined by the International Study of Kidney Disease in Children (ISKDC) [34].

Sustained remission is remission with no relapse for at least six months [34].

Initial resistance (steroid-resistant NS-SRNS).: Failure to achieve complete remission after 8 weeks of corticosteroid therapy as defined by ISKDC [33].

Secondary steroid resistant NS refers to the development of steroid resistance in a child with a previous steroid sensitive disease [33,36].

Relapse is when there is there is ≥2+ protein on urine dipstick for 3 consecutive days [33].

Frequent relapse is when there are ≥2 relapses in the first 6 months after the presentation or ≥4 relapses within any 12-month period [33].

Infrequent relapse is when children experience less than three relapses in a year [33].

Steroid-dependent NS is when children relapse whilst on steroid therapy or within 14 days of discontinuation of steroid therapy [33].

ISKDC steroid regimen used was 60mg/m2 once daily (single morning dose) for 28 days, followed by 40 mg/m^2 given on an alternate day for a further 28 days [33].

The ISKDS steroid regimen for infrequent relapse is prednisolone 60 mg/m^2 daily until urinary remission (three consecutive days of zero or trace proteinuria), followed by 40 mg/m^2 on an alternate day for 14 doses over a 28-day period [33].

Steroid dependence was treated with the addition of levamisole (2.5 mg/kg/day) on alternate days or oral cyclophosphamide. Steroid resistance was treated with alternate day steroid at 30 mg/m^2 with cyclosporine or mycophenolate. We generally prefer cyclosporine [37] rather than mycophenolate except in children with impaired GFR in CKD.

Supportive treatment includes the use of cimetidine and omeprazole while on steroid therapy 40–60 mg/m^2, diuretics (frusemide, spironolactone and hydrochlorothiazide) for oedema, intravenous hydralazine and nifedipine/amlodipine for hypertension, and angiotensin-converting enzyme inhibitors for SRNS.

The stages of CKD in children with urinary albumin excretion rate of ≥30 mg/24 hour or abnormal renal ultrasound or abnormal urinary sediment with impaired estimated GFR (eGFR) for more than 3 months were as follows: eGFR in ml/minute/1.73 m^2 G1; ≥90, G2; 60–89, G3a; 45–59, G3b; 30–44,G4;15–29 and G5 < 15 [38].

Hypertension was defined as systolic and or diastolic blood pressure greater than the 95th centile for age, gender and length using nomogram published in the fourth report of the National High Blood Pressure Education Group [39].

Significant microhaematuria is red blood cells (RBC) ≥5/high power field.

Socioeconomic status (SES) stratification was done using the one proposed by Oyedeji which employs the educational status and occupation of parents [40]. SES was classified into high, medium and low based on the occupation and level of education of the parents.

Renal biopsies were performed only for SRNS and four samples (for children ≥ 15 years who met inclusion criteria for Human Hereditary and Health (H3) Africa Kidney Disease Research Network Cohort Study) were analysed at Department of Pathology, Michigan Medicine, 1500 E Medical Center Dr Ann Arbor, MI 48109 for light, electron and immunofluorescent microscopy.

Data analysis

Statistical analysis was done with the SPSS version 16. Characteristics were summarised using means for normally distributed variables and medians for those that were not. Means were compared using an unpaired *t*-test, and Mann–Whitney was employed for the medians. The proportions of the categorical variables were compared using Chi-Square or Fisher's exact as appropriate. A simple description of the clinicopathology of the NS was done. *p*-values less than 0.05 was considered as significant.

RESULTS

A total of 46 children with NS were seen over the study period, increasing from 9 in 2016 to 11 in 2017 and 26 in 2018. The mean age was 8.2 ± 4.4 years with ages in the range of 17 months to 18 years. The peak burden of NS was seen in the age group 6–10 years. There were 37 males (M) and 9 females (F) with a male: female ratio of 4.1:1.

Table 1 reveals some clinicodemographic characteristics of the subjects. Majorities (11, 23.8%) of the NS children were of Ibo ethnic group, of the low socioeconomic group (20, 43.5%) and Christian (33, 71.7%). Forty-one (89.1%) of the subjects had INS, whereas, secondary NS were found in 5 (10.9%) including Hepatitis B infection, sickle cell anaemia (Haemoglobin SS), haemolytic-uraemic syndrome and two with post-infectious chronic glomerulonephritis. Low C3 (and normal C4) levels were also demonstrated in the child with sickle cell anaemia and in the other two with post-streptococcal glomerulonephritis. No *P. malariae* band form was seen in thick and thin blood film, but *P. falciparum* (1+) was seen in subjects with Hepatitis B infection and sickle cell anaemia.

Table 2 reveals the atypical presentation among the subjects. A greater (24, 52.2%) number of the subjects presented with varying features of atypical NS, with hypertension and gross haematuria seen in 16 (34.8%) and 5 (10.9%), respectively. Thirteen were classified as atypical because they were more than 12 years of age. No infantile NS was seen. Of the five with gross haematuria, one child had sickle cell anaemia (Haemoglobin SS), one with the haemolytic-uraemic syndrome, one with urinary tract infection and two with post-streptococcal glomerulonephritis. Low eGFR was seen in 11 (23.9%) children, two of whom

Table 1. Some clinicodemographic characteristics of the subjects with nephrotic syndrome.

Variables	Number	%
Age groups		
0–5 years	14	30.4
6–10	17	37.0
≥11	15	32.6
Gender		
Male	37	80.4
Female	9	19.6
Religion		
Christianity	33	71.7
Islam	13	28.3
Socioeconomic class		
Low	20	43.5
Medium	11	23.9
High	15	32.6
Ethnicity		
Ibo	11	23.8
Hausa	7	15.2
Yoruba	7	15.2
Others		
Bassa	5	10.9
Ebira	3	6.5
Fulani	2	4.3
Zarma	2	4.3
Amo	1	2.2
Tiv	1	2.2
Gbagyi	1	2.2
Idoma	1	2.2
Bura	1	2.2
Tarok	1	2.2
Ogori	1	2.2
Birom	1	2.2
Igala	1	2.2
Steroid responsiveness		
SSNS	34	73.9
SRNS	12	26.1
Secondary		
Yes*	5	10.9
No	41	89.1
Clinical presentations		
Typical	22	47.8
Atypical	24	52.2

*=1 Hepatitis B positive, 1 sickle cell anaemia (Haemoglobin SS), 1 haemolytic uraemic syndrome, 2 post-infectious glomerulonephritis.
SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

Table 2. Atypical clinical presentations of nephrotic syndrome.

Characteristics	Number (%)
Hypertension	7.0 (15.2)
Age	3.0 (6.5)
Age + hypertension+ deranged eGFR	3.0 (6.5)
Age+hypertension+gross haematuria + deranged eGFR	2.0 (4.3)
Hypertension + gross haematuria +deranged eGFR	2.0 (4.3)
Gross haematuria	1.0 (2.2)
Gross haematuria + deranged eGFR	1.0 (2.2)
Age + hypertension + gross haematuria + low C3* + deranged GFR	1.0 (2.2)
Age + hypertension+ low C3*	1.0 (2.2)
Age + hypertension	1.0 (2.2)
Low C3*+ hypertension+ deranged GFR	1.0 (2.2)
Deranged eGFR	1.0 (2.2)

*C3/C4 values were only available for 3 of the 46 subjects.
eGFR, estimated glomerular filtration rate.

presented in CKD stages 3 and 4, two with post-streptococcal glomerulonephritis and the remaining seven in AKI. Three of the AKI were supported with haemodialysis (maximum of two sessions) before steroid therapy and four were managed conservatively. All the AKI cases later proved to be SSNS

Table 3 compares the socio-demographic and the clinical features between SSNS and SRNS. Of the 46 NS, most (34, 73.9%) responded to the steroid, with a median day of responsiveness being 20 days and between 5 to 42 days. Seven (7/34, 20.6%) were late responders, who went into remission between 29 and 42 days on low-dose alternate-day steroid. SSNS was also seen predominantly (24/34, 70.6) in those aged 10 years and below, and in males (28/34, 82.4%), although these findings were not statistically significant. Only two (2/5, 40%) of the secondary NS responded, whereas steroid responsiveness occurred in 32 (32/41, 78%) of the INS. In addition, SSNS occurred more (18/34, 52.9%) among those with atypical presentation than those with typical features (16/34, 47.1%). Varying degrees of oedema was the commonest

Table 3. Sociodemographic and clinical features comparisons between steroid-sensitive and steroid-resistant nephrotic syndrome subjects at presentation.

Sociodemographic features	Steroid-sensitive nephrotic syndrome (%)	Steroid-resistant nephrotic syndrome (%)	*P-value*
Age (mean age in years ± SD)	7.71 ± 4.37	9.46 ± 4.58	0.240
Age group (years)			
0–5	12 (85.7)	2(14.3)	
6–10	12 (70.6)	5(29.4)	0.470
≥11	10 (66.7)	5(33.3)	
Gender			
M	28 (75.7)	9 (24.3)	0.580
F	6 (66.7)	3 (33.3)	
Religion			
Christianity	23 (69.7)	10 (30.3)	0.300
Islam	11 (84.6)	2 (15.4)	
Socioeconomic class			
Low	14 (70.0)	6 (30.0)	
Medium	10 (90.9)	1 (9.1)	0.330
High	10 (66.7)	5 (33.3)	
Ethnicity			
Ibo	7 (63.6)	4 (36.4)	
Hausa	6 (85.7)	1 (14.3)	0.440
Yoruba	4 (57.1)	3 (42.9)	
Others	17 (81.0)	4 (19.0)	
Atypical	18 (81.8)	4 (18.2)	0.240
Typical	16 (66.7)	8 (33.3)	
Secondary NS			
Yes	2 (40)	3 (60)	0.070
No	32 (78)	9 (22)	
Clinical features			
Hypertension			
Yes	9 (56.2)	7 (43.8)	0.040
No	25 (83.3)	5 (16.7)	
Sepsis			
Yes	12 (75)	4 (25)	0.900
No	22 (73.3)	8 (26.7)	
Symptomatic oedema			
Yes*	11 (78.6)	3 (21.4)	0.630
No	23 (71.9)	9 (28.1)	
Anaemia			
Yes	7 (87.5)	1 (12.5)	0.330
No	27 (71.1)	11 (28.9)	

(Continued)

Table 3. (Continued)

Sociodemographic features	Steroid-sensitive nephrotic syndrome (%)	Steroid-resistant nephrotic syndrome (%)	*P-value*
Peritonitis			
Yes	5 (71.4)	2 (28.6)	0.870
No	29 (74.4)	10 (25.6)	
Gross haematuria			
Yes	5 (100)	0	0.160
No	29 (70.7)	12 (29.3)	
UTI			
Yes	2 (100)	0	0.390
No	32 (72.7)	12 (27.3)	

*=All the children had some degree of oedema, but symptomatic in 14 (2 with oozing fluids from the skin, 7 with spontaneous peritonitis and the remaining 5 with difficulty in breathing and scrotal/vulva oedema).
F, female; M, male; NS, nephrotic syndrome; SD, standard deviation; UTI, urinary tract infection.

(100%) clinical feature and it was symptomatic in 14 (30%) cases. Other clinical presentations included hypertension in 16 (34.8%), sepsis in 16 (34.8%), anaemia in 8 (17.4%), gross haematuria in 5 (10.9%) and urinary tract infection (UTI) in 2 (4.3%). *Escherichia coli* were the bacteria isolated in the two UTI cases. The median systolic blood pressure was 100 (IQR of 42.5) mmHg, while the median diastolic pressure was 60 (IQR = 36.3) mmHg. For those who were hypertensive, the mean systolic blood pressure was 136.25 ± 14.1 mmHg and the mean diastolic pressure was 93.4 ± 10.8 mmHg. The median weight and length at admission were 30.5 (10.9–62.0) kg and 123 (83.5–170.0) cm, respectively. The median body mass index was 20.2 (15.4–21.5) kg/m^2, and no subject was overweight or obese. When the clinical presentations were compared between SSNS and SRNS, only hypertension (more among the SSNS) was statistically significantly, (p value = 0.04).

Table 4 depicts the laboratory findings of the subjects. The mean serum albumin was 17.9 ± 5.6 g/l with a range of 9–29 g/l. The median cholesterol was 4.8 (IQR of 2.43) mmol/l, with a range of 2.4–16.6 mmol/l. For spot urine protein/creatinine ratio, the median was 730 (IQR of 827) and a range of 214 to 5,530 mg/mmol. Hypoalbuminaemia was seen in 38 (82.6%), hypercholesterolaemia in 19 (41.3%), hypocalcaemia in 27 (58.7%), microscopic haematuria in 19 (41.3%), hyponatraemia in 12 (26.1%) and hypokalaemia in 7 (15.2%). Furthermore, all the parameters (except eGFR and cholesterol) were higher in SSNS than in SRNS, but, none was statistically significant.

The histopathological findings were available for 5 (41.7 %) of the 12 SRNS, 2 declined renal biopsy and 5 were lost to follow-up. Four biopsies were done at the UATH and shipped abroad for interpretations. Three available results of the shipped specimens were minimal change disease (1/5, 20%), severe interstitial fibrosis/glomerulosclerosis (1/5, 20%) and primary focal segmental glomerulosclerosis (1/5, 20%). The subject with severe interstitial fibrosis also came in CKD Stage 3. The result is still pending for the fourth child, as at the time of this report. One child was referred to us with a report of focal segmental glomerulosclerosis and the same result was found in the child that had renal transplantation prior to transplant at a private hospital in Abuja, Nigeria. In total, focal segmental glomerulosclerosis accounted for three out of five (60%) renal pathology.

Table 5 shows the outcome of the subjects on follow-up. Follow-up period varied between 6 months and 2 years, with a mean follow-up period of 9 months. Thirty (88.2%) of the SSNS were still on follow-up, four out of whom had had infrequent relapses and one relapsed frequently (relapse rate

Table 4. Comparison of laboratory findings between steroid-sensitive and steroid-resistant nephrotic syndrome subjects at presentation.

Laboratory findings	Steroid-sensitive nephrotic syndrome (%)	Steroid-resistant nephrotic syndrome (%)	*P*-value
Hypoalbuminaemia			
Yes	27 (71.1)	11 (28.9)	0.340
No	7 (87.5)	1 (12.5)	
Hypocalcaemia			
Yes	19 (70.4)	8 (29.6)	0.510
No	15 (78.9)	4 (21.1)	
Microhaematuria			
Yes	15 (68.2)	7 (31.8)	0.620
No	19 (79.2)	5 (20.8)	
Hypercholesterolaemia			
Yes	13 (68.4)	6 (31.6)	0.470
No	21 (77.8)	6 (22.2)	
Hyponatraemia			
Yes	8 (66.7)	4 (33.3)	0.510
No	26 (76.5)	8 (23.5)	
Deranged eGFR			
Yes	7 (63.6)	4 (36.4)	0.370
No	27 (77.1)	8 (22.9)	
Hypokalaemia			
Yes	6 (85.7)	1 (14.3)	0.440
No	28 (71.8)	11 (28.2)	
Metabolic acidosis			
Yes	3 (75)	1 (25.0)	0.960
No	31 (73.8)	11 (26.2)	
Hypernatraemia			
Yes	3 (100)	0	0.290
No	31 (72.1)	12 (27.9)	
Hyperkalaemia			
Yes	2 (100)	0	0.390
No	32 (72.7)	12 (27.3)	
Yes	2 (100)	0	0.390
No	32 (72.7)	12 (27.3)	
Hypercalcaemia			
Yes	2 (100)	0	0.390
No	32 (72.7)	12 (27.3)	
eGFR –median (IQR) SD) ml/min/1.73m^2	106 (101.1)	144.5 (207.8)	0.750

(Continued)

Table 4. *(Continued)*

Laboratory findings	Steroid-sensitive nephrotic syndrome (%)	Steroid-resistant nephrotic syndrome (%)	*P*-value
Albumin-mean± SD g/l	18 ± 5.87	17.75 ± 5.2	0.890
Cholesterol-median (IQR) mmol/l	4.36 (1.91)	5.35 (4.49)	0.290
Sodium (mean± SD)	138 ± 8.25	136.5 ± 11.75	0.760
Potassium(mean± SD)	4.32 ± 1.036	4.25 ± 0.62	0.820
Calcium(mean± SD)	2.06 ± 0.34	1.99 ± 0.099	0.490
Chloride(mean± SD)	103.32 ± 6.91	101.92 ± 9.28	0.580
Bicarbonate(mean± SD)	19.79 ± 4.58	21.28 ± 3.75	0.330
sUPCR-median (IQR) mg/mmol	426.5 (646)	663 (685)	0.240
Creatinine-median (IQR)	49.0 (53.0)	44 (112.3)	0.980
pH (mean± SD)	6.21 ± 0.81	6.25 ± 0.45	0.860
Specific gravity (mean± SD)	1.0018 ± 0.0072	1.0008 ± 0.0029	0.670
PCV(mean± SD)	33.41 ± 4.38	34.92 ± 5.35	0.340

eGFR, estimated glomerular filtration rate; IQR=interquartile range; PCV=packed cell volume; SD=standard deviation, eGFR=estimated glomerular filtration rate, sUPCR=spot urine protein/creatinine ratio, PCV=packed cell volume, IQR=interquartile range.

Table 5. Outcome of treatment after 6 months of follow-up.

Outcome	Number
Steroid-sensitive* still on follow-up	30
Steroid-resistant still on follow-up	2
Lost to follow-up^	9
Complications of steroid&	10
End-stage kidney disease (ESKD)+	3
Death#	4

*=4 infrequent relapsers and 1 frequent relapser; ^= 5 from steroid-resistant and 4 from steroid-sensitive group; &= 7 moon facing, 2 obesity/striae, and 1 new-onset hypertension; +=1 had renal transplantation and doing clinically well; #=2 of ESKD while on maintenance dialysis, 2 of the steroid-resistant nephrotic syndrome also died acutely from hypertensive encephalopathy.

of 16.7%, 5/30). These five relapses also occurred in boys <11 years, and all had remission after 14 days of starting prednisolone. Four of SSNS were lost to follow-up. Complications attributable to prednisolone included moon- facing (7), new-onset obesity/striae (2), and new-onset hypertension (1). All these complications occurred in SSNS.

For the SRNS, two were still on follow-up, one on mycophenolate and the other on cyclosporine, with a partial response of proteinuria in both. Five of the SRNS were lost to follow-up. Two of the three SRNS that progressed to ESKD died. One died after seven sessions of maintenance haemodialysis, and the other, after 24 sessions. Cause of death in the two was acute pulmonary oedema when dialysis could not continue. The other ESKD (a 9-year-old boy) survived after renal transplantation in a private hospital in Abuja. He is presently on tacrolimus, mycophenolate and prednisolone. Mortality also occurred in two SRNS who died during admission for hypertensive encephalopathy. Therefore, the overall mortality was 8.7% from four deaths among the SRNS subjects only.

DISCUSSION

This is a report of 46 NS Nigerian children aged 17 months to 18 years (mean age of 8.2 ± 4.4 years) who were all treated with prednisolone at presentation using the ISKDC regimen and who have been followed-up for 6 months to 2 years.

The complications attributable to prednisolone were the moon- facing, new-onset obesity/striae and new-onset hypertension.

In this cohort, NS occurred predominantly more in males than in females in a ratio of 4.1:1. Similar male predominance in CNS had been reported earlier in Nigeria [21–23,25,30] and elsewhere [41,42]. However, Anochie et al. [24] reported no gender difference in the prevalence of NS in their own study. No reason has been adduced for this male preponderance.

The high steroid responsiveness of 73.9% in this study (78% among INS) agrees with the studies of Ladapo et al. [30], Anochie et al. [24] and Asinobi et al. [19] that also reported a respective high steroid responsiveness of 75.9%, 80% and 60% among ethnically black Nigerian children. Our study is unique because the high steroid responsiveness occurred despite a relatively older mean age (8.2 years) of our subjects, unlike the earlier studies that reported the high steroid responsiveness among younger children with mean ages of 5.9 years [30], 5.8 years [24] and ≤ 5 years [19]. Whereas the young age predilection in these earlier studies [19,24,30] may be similar to European and North American children with NS with high steroid sensitivity [7,13–15]; our study may be highlighting a crop of Black children with NS with increasing sensitivity to steroid even at an older age. The finding of high steroid sensitivity in this study is also instructive as this exists despite the high record of atypical features of NS including hypertension (66.7%), low eGFR (23.9%) and gross haematuria (20.8%). Nevertheless, INS was still the main aetiological type (89.1%) in this cohort. Gross hematuria is not associated with MCNS [35]. While hypertension prior to corticosteroid is unusual with MCNS [43], hypertension has been reported in 50 % of children with focal segmental glomerulosclerosis (FSGS) [43]. In this study, we noticed that hypertension was significantly more among the SSNS. The hypertension is also not related to overweight and/or obesity as none was present among our subjects. Apart from the hypertension presenting with other atypical features of NS in this report, we could not readily explain this finding except to suggest that the hypertension may be essential in these ethnically black children.

The rate of relapse in this cohort was 16.7%, a value lower than 93.8% reported in Port Harcourt, Nigeria [24] and 56.3% in Ghana [44]. While all the relapses occurred in boys < 11 years who all had remission after 14 days of starting prednisolone, hitherto, the frequency of relapse has been noted to be higher in children <3-4 years at onset of NS, who had delayed time to remission (after 7-9 days) and who had occurrence of an early relapse (in the first six months after initial treatment)[24,45–47].

Our cohort has a short mean follow-up period of 9 months, and we are mindful of the limitation in interpreting the preliminary findings of the high steroid responsiveness. Although renal biopsy is only done at steroid resistance, we are constrained to assume that MCNS may be the renal lesion in children that responded to steroid at this time.

Steroid resistance is 26.1% in this study and FSGS also predominates among the few SRNS that had renal biopsies. In actual fact, electron microscopy confirmed one of the cases of the FSGS to be of the primary type. We are however unable to offer genetic testing to this child. Going by the recent publication of Pelletier et al. [48] that documented the recurrence of NS in the renal graft to be 0% in monogenic NS, the knowledge of genetic testing, in this case, would have been beneficial to the clinical management of this patient.

Hitherto, geographical variations in Nigeria reported steroid resistance at higher values, between 35 % and 92% [22,25,26,49,50]. This steroid resistance parallels the underlying renal histopathology which reveals a rarity of MCD but a varying burden of MPGN, focal mesangial proliferative glomerulonephritis lesion, and FSGS [22,25,26,49,50]. In other settings in Africa, steroid resistance was 50% in Ghana [44] and 86% in South African black children [18]. There is also an increasing burden of steroid resistance in Europe, USA and Asia, a finding that is also consistent with an emerging underlying burden of FSGS [51–55].

Hypercholesterolaemia is not a common feature in the study as it is seen in 41.3% of the patients. This value was higher than 17.5% reported by Ibadin and Abiodun [21] but lower than 94.4% by Ugwu in Nigeria [56]. The ISKDC also found

hypercholesterolaemia in 95% of children with minimal change lesion and in 60% of children with other histologic types [43]. A low oncotic pressure resulting from hypoalbuminaemia is a known stimulant for hypercholesterolaemia [35]; however, the rare finding of hypercholesterolaemia contrasts with hypoalbuminaemia of 82.6% in this cohort. We agree with Ibadin and Abiodun that had earlier linked a lower hypercholesterolaemia finding in NS to variations in lipid food intake among subjects with NS [21]. In addition, hypercholesterolaemia may therefore not be an important feature in the diagnosis of NS in our setting. Our findings also agree with Trachtman et al. [35] that identified massive proteinuria as the only criterion essential for the diagnosis of NS [35].

SNS is seen in only five children, including Hepatitis B infection, sickle cell anaemia, haemolytic-uraemic syndrome and post-infectious chronic glomerulonephritis (two cases). This low prevalence of SNS will also argue in favour of the high steroid responsiveness in this study. We did not document any case of quartan malaria nephropathy (QMN) similar to the findings of Ladapo et al. [30] and Olowu et al. [50]. The rarity of SNS in this cohort also supports the earlier studies that had suggested a reduction in the incidence of infectious diseases as a secondary cause of NS [30,34]. Thus, our finding contrasts the earlier studies (done in the 1960s, 1970s and in 1990) in Nigeria, where QMN was a prominent cause of childhood NS [20–23,28]. The reasons for the recent rarity of QMN had been summarised earlier by Olowu et al. [50] to include " improved living standards, healthcare access, better understanding of clinical features of malaria and treatment and ready access to antimalarials contrary to what it was in the 1960s and 1970s when Medicare access was poor" [50]. We cannot, however, over-emphasise the contributions of other infections, such as Hepatitis B, HUS and post-infectious glomerulonephritis to SNS as an improvement in the control of these infections would largely reduce the burden of SNS in our setting. Sickle cell anaemia (SCA) is the commonest single gene disorder affecting up to 2%–3% of newborns and the sickle cell trait also affects up to a quarter of the population (22%–25%) [57–60]. Glomerular endothelial lesions from constant sickling and microinfarcts eventually leading to significant proteinuria and the NS have been reported in children and adults with SCA [24,30] and SCA is now being recognised as a common cause of SNS in Nigerian children [30,50,61].

The overall mortality in this study was 8.7% accruing from four deaths among the SRNS subjects. Expectedly, progression to CKD/ESKD is the norm with SRNS [6]. In this cohort, two deaths occurred from acute pulmonary oedema when maintenance dialysis could not be continued for ESKD from lack of fund. The two other deaths occurred during re-admission for hypertensive encephalopathy (hypertension predated steroid commencement). No death is attributable to the use of prednisolone. One child with SRNS in ESKD had been transplanted and he is doing very well a year after the renal transplantation.

The rather small sample size in this cohort is a major limitation of the present study. However, being a prospective study, it allows for complete data keeping except when some investigations' results (C3 and C4) are unavailable for lack of fund. The finding of primary FSGS on electron microscopy may also be supporting a possibility of genetic abnormalities of the glomerular filtration barrier because the patient was primarily resistant to the steroid, an indication that the aetiology may not be immune-mediated [48]. However, the opportunity for genetic testing does not exist in our centre. We are also cautious in the interpretation of the steroid responsiveness and the remission rates as follow-up period is short (a mean period of 9 months).

CONCLUSIONS

This study would sum up to indicate that Nigerian children with NS, regardless of age and other atypical features, have a high steroid responsiveness at 73.9%. It shows that the majority is INS and that mortality is high among those with SRNS from ESKD and hypertensive encephalopathy. The study is supporting a notion that steroid responsiveness is increasing among ethnically black Nigerian children [19,24,30] and that pre-treatment renal biopsy may be unwarranted.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ETHICAL APPROVAL

Ethical clearance and approval of the study were obtained from the Health Research Ethics Committee (HREC) of the UATH, Abuja. The procedure of the study was also in accordance with the ethical standards of the HREC of the UATH and in accordance with the Helsinki Declaration of 1975, as revised in 2008. Signed informed consent for participation and publication of medical details were obtained from the guardians.

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