ORIGINAL ARTICLE

CLINICAL FEATURES AND OUTCOME OF CHILDHOOD NEPHROTIC SYNDROME IN CALABAR, NIGERIA

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ABSTRACT

BACKGROUND

Nephrotic syndrome (NS) is a common childhood renal problem caused by impaired glomerular function, resulting in protein leakage into the urine. Most are idiopathic and respond to steroid therapy, however, steroid-sensitivity varies across geographical regions. The aim is to evaluate the clinical characteristics, the natural history, steroid responsiveness and outcome among children in Calabar, Nigerian.

METHODS

A retrospective study carried out in the University of Calabar Teaching Hospital (UCTH), Calabar. Case folders of all children with Nephrotic Syndrome admitted from August, 2016 to July, 2022 were reviewed. Information obtained include age, sex, duration of illness before presentation, clinical features, urea/electrolyte/ creatinine results, duration of hospital stay, and outcome. Data was analyzed with SPSS version 22.0 and p-value ≤ 0.05 was significant.

RESULTS

Out of the one hundred and eighty-one renal patients, 30 (16.6%) had Nephrotic Syndrome, aged 2.4 to 17 years, mean age 11.3 ± 4.0 years and a M:F ratio of 1.5:1. Oedema was the commonest feature affecting mainly the face, abdomen, leg and scrotum. There were few atypical features of fever, cough, haematuria and hypertension. Most cases of NS were steroid sensitive (73.3%). Steroid Resistant NS and Frequent Relapse NS were 16.7% and 10.0% respectively. Many of the Steroid Resistant NS progressed to Chronic Renal Failure and End-Stage Renal Disease. Most cases were discharge (90.0%), three left against Medical Advice and none died, but a good number were lost to follow-up.

CONCLUSION

Oedema is the commonest presentation of Nephrotic syndrome in Calabar. Most were Steroid Sensitive NS with few Steroid Resistant NS and Frequent Relapse NS. Early presentation and prompt treatment enhanced our good outcome.

KEY WORDS

Nephrotic syndrome, Oedema, Prednisolone.

INTRODUCTION

Nephrotic syndrome (NS) is a common childhood renal problem, caused by impaired glomerular function, leading to protein leakage into the urine.

It is Characterised by heavy proteinuria, hypoalbuminaemia, hypercholesterolemia and Generalized oedema.[1,2]

The incidence of Childhood Nephrotic Syndrome (CNS) globally ranges from 1.2 to 16.9 cases per 100,000 children; while in Africa is between 4.6 to 13 cases per 100,000. [3-7] In Calabar, it accounts for 22.7-30.7% of all renal disorders in children.[8,9]

Oedema is a common presenting complaint in children with nephrotic syndrome. It results in multiple hospitalizations, increased morbidity, discomfort, impaired mobility, and increased risk of soft-tissue infection.[10]

Worldwide, majority of childhood nephrotic syndrome are idiopathic and respond to steroid therapy, hence, called steroid-sensitive nephrotic syndrome (SSNS).[11] However, steroid-sensitivity varies across geographical regions depending on disease type, aetiology, and underlying genetics. [11-13]

In Nigeria, earlier studies did not show a favourable response to steroid therapy among children with NS, [14,15] but, recent studies from several regions in the country are documenting high and increasing rates of steroid responsiveness. [16-18] Unfortunately, there is still a paucity of information on clinical characteristics, the natural history, steroid responsiveness of NS and outcome among Nigerian children especially in the South-South geo-political zone.[16] Hence, this current study looked into these areas concerning childhood nephrotic syndrome in Calabar.

METHODOLOGY

This was a retrospective study carried out in the Nephrology Unit, Department of Paediatrics, University of Calabar Teaching Hospital (UCTH), Calabar. The hospital is located in Calabar, the capital of Cross River State in the South-South geopolitical zone of Nigeria. It is a referral center in the state and also serves the neighbouring states of Akwa Ibom, Abia and Benue. The case folders of all children with nephrotic syndrome admitted to the children's ward of UCTH from August, 2016 to July, 2022 were reviewed. Information obtained included age, sex, duration of illness before presentation to the hospital, clinical features, urea/electrolyte/ creatinine results, duration of hospital stay, and outcome. Also, the total number of admissions for renal disorders during the study period was noted.

Data collected using the case folders were checked for accuracy and entered into Statistical Package for Social Sciences (SPSS) version 20.0, 2011 and analysed with the same software. Descriptive statistics such as frequencies and percentages, means, standard deviations, and mode were computed. Inferential statistics such as chi-square test and Fisher's exact test were computed. All analysis was done at a 95% level of significance, p value ≤ 0.05. Ethical clearance was obtained from the University of Calabar Teaching Hospital Health Research Ethics Committee, Calabar, Cross River State.

DEFINITION OF TERMS

Nephrotic Syndrome Diagnosis: Made when degree of proteinuria in dipstick urinalysis was 3+ or 4+, or exceeding 40 mg/m^2/hour or spot-urine protein-creatinine ratio ≥ 2.0, hypoalbuminemia with a serum albumin less than 25 g/L and hyperchloesterolaemia > 250mg/dl.[1,19,20]

Treatment: Tab prednisolone was given at 60mg/m^2/day or 2mg/kg/day (Max dose 80mg) in 2 or 3 divided doses for at least 4 weeks. (4 to 6 weeks). After, the initial 4-6 weeks course, the prednisolone dose is tapered to 40mg/m^2 or 1.5mg/kg (Max dose 40mg) given alternate day as a single morning dose. The alternate day dose is then slowly tapered and discontinued over the next 2-5 months. Hence, the minimum total duration of treatment is 12weeks.[20, 21]

Remission: Nil or trace proteinuria by dipstick for three consecutive days in patient on steroid therapy[21,22]

Steroid Sensitive Nephrotic Syndrome (SSNS): Achieving remission within four to six weeks of daily oral prednisolone. Early responders achieved remission within the first four weeks while late responders achieved remission after four weeks.[20-22]

Steroid Resistant Nephrotic Syndrome (SRNS): Failure to achieve remission after eight weeks of appropriate oral daily dose prednisolone.[21]

Relapse: Recurrence of 100 mg/dl (≥ 2+) proteinuria by dipstick for three consecutive days and oedema after achieving remission. [22]

Frequent Relapsing Nephrotic syndrome (FRNS): Two or more relapses within six months of initial response or four or more relapses in any twelve-month period.[21,22]

Alternative agents: Patients for alternative agents include: steroid dependent, steroid resistant and frequent relapsers. [21] Alternative agents used include:

Cyclophosphamide: Dose: 2-3mg/kg/24hours given as single oral dose for 8-12weeks, alternate day prednisolone continued during the course of cyclophosphamide administration.

Cyclosporin A: Dose: 5mg/kg/day or 100-150mg/m^2/day.

Levamisole: Dose: 2-2.5mg/kg on alternate day for 1-2 years. It is given together with alternate day prednisolone.

Secondary NS (SNS): Refers to proven aetiology extrinsic to the kidney eg HIV and Hepatitis B infections, Sickle cell anaemia, nephrotoxic agents like mercury containing compounds. [19,21]

Idiopathic NS (INS) is when NS is not congenital or secondary.[19,22]

Hypertension: Blood pressure greater than or equal to the 95th percentile to less than 95th percentile + 12mmHg, or 130/80 to 139/89 mmHg (whichever is lower) .[23]

RESULTS:

Out of the one hundred and eighty-one renal patients admitted during the six years period of the study, 30 (16.6%) had nephrotic syndrome. These children were aged 2.4 to 17 years, mean age 11.3 ± 4.0 years and a male: female ratio of 1.5:1 (Table I)

TABLE I:
AGE AND SEX DISTRIBUTION OF CHILDREN WITH NEPHROTIC SYNDROME (NS)

Age Range (Years)	Sex		Total n (%)	Test of Statistics	*p*-value
	Male n (%)	Female n (%)			
2-5	2(6.7)	3(10.0)	5(16.7)	Fisher Exact Test	1.000
6-9	4(13.3)	2(6.7)	6(20.0)		
10-13	5(16.7)	4(13.3)	9(30.0)		
14-17	7(23.3)	3(10.0)	10(33.3)		
TOTAL	**18(60.0)**	**12(40.0)**	**30(100.0)**		

TABLE II:
TYPE OF NEPHROTIC SYNDROME IN THE STUDY

TYPE	FREQUENCY(N)	PERCENTAGE (%)
Primary or Idiopathic	22	73.3
Secondary Nephrotic Syndrome		
Sickle cell anaemia (HbSS) with Nephrotic Syndrome	1	3.3
HIV Associated Nephropathy	2	6.7
Disseminated Tuberculosis with Nephrotic Syndrome	2	6.7
Post-infectious Glomerulonephritis	3	10.0
TOTAL	**30**	**100.0**

TABLE III:
CLINICAL FEATURES OF NEPHROTIC SYNDROME

Clinical Presentation	Frequency (N)	Percentage (%)
Facial Swelling	30	100.0
Abdominal Swelling	28	93.3
Leg Swelling	26	86.7
Generalized Body Swelling	15	50.0
Frothy Urine	5	16.7
Haematuria	3	10.0
Hypertension	3	10.0
Reduced Urinary Output	8	26.7
Frequent Micturition	2	6.7
Dysuria	1	3.3
Fever	6	20.0
Abdominal Pain	4	13.3
Vomiting	4	13.3
Cough	6	20.0

* Multiple response

TABLE IV:
UREA, ELECTROLYTES AND CREATININE (U/E/Cr) OF CHILDREN WITH NS
The three patients with abnormal U/E/Cr had chronic kidney disease, one in stage IV and the other two in stage V (End-stage renal disease).

Urea/Electrolyte/Creatinine	Frequency (N)	Percentage (%)
Normal	27	90.0
Abnormal	3	10.0
Total	**30**	**100.0**

TABLE V:
TREATMENT RECEIVED FOR NS

Treatment Received	Frequency (N)	Percentage (%)
Prednisolone	29	96.7
Furosemide	20	66.7
Hydrochlorothiazide	26	86.7
Enalapril	25	83.3
Cyclophosphamide	5	16.7
Levamisole	1	3.3
Spironolactone	5	16.7
Aldomet	1	3.3
Nifedipine(Sublingual)	1	3.3
Amlodipine	9	30.0
Augmentin	8	26.7
Ceftriaxone	6	20.0
Pooled plasma	7	23.3

** Denominator = 30

TABLE VI:
AGE RANGE AND SEX WITH NEPHROTIC SYNDROME RESPONSE TO TREATMENT.

Variable	Nephrotic Syndrome Response to Treament			Total	Test of Statistics	p-value
Age group(Years)	**SSNS n(%)**	**SRNS n(%)**	**FRNS n(%)**			
2-5	4(13.3)	0(0.0)	0(0.0)	4(13.3)	Fisher's Exact Test	0.820
6-9	5(16.7)	0(0.0)	0(0.0)	5(16.7)		
10-13	6(20.0)	2(6.7)	1(3.3)	9(30.0)		
14-17	7(23.3)	3(10.0)	2(6.7)	12(40.0)		
Total	**22(73.3)**	**5(16.7)**	**3(10.0)**	**30(100.0)**		
Sex						
Male	13(43.3)	3(10.0)	2(6.7)	18(60.0)	Fisher's Exact Test	1.000
Female	9(30.0)	2(6.7)	1(3.3)	12(40.0)		
Total	**22(73.3)**	**5(16.7)**	**3(10.0)**	**30(100.0)**		

DURATION OF ILLNESS BEFORE ADMISSION AND OUTCOME

Among the 27 discharged patients (Table VII), SSNS on follow-up were 17(63.0%), SRNS on follow-up 2(7.4%), while 8(29.6%) were lost to follow-up. Three left against medical advice (LAMA) and none died.

TABLE VII:
DURATION OF ILLNESS BEFORE ADMISSION AND OUTCOME

Duration of Illness Before Admission (Weeks)	OUTCOME		TOTAL N(%)	TEST OF STATISTICS	*p*-value
	Discharge N(%)	LAMA N(%)			
1-4	22(73.3)	2(6.7)	24(80.0)	Fisher's exact Test	0.501
5-8	2(6.7)	1(3.3)	3(10.0)		
9-12	2(6.7)	0(0.0)	2(6.7)		
>12	1(3.3)	0(0.0)	1(3.3)		
TOTAL	**27(90.0)**	**3(10.0)**	**30(100.0)**		

DISCUSSION:

Nephrotic Syndrome (NS) accounted for 16.6% of renal admissions in this study. However, this was low compared to the 30.7% and 22.7% obtained in previous studies in Calabar carried out 23 and 7 years ago respectively.[8,9] The reason for this reduction is not clear. It could be due to the decline in the number of patients over the past 2 decades. There is also a change in the ranking of the aetiology of renal disease in our environment in which urinary tract infections now placed above NS.[8,24] Nephrotic syndrome is still among the commonest renal disorders in our environment as shown in studies conducted in Port Harcourt[24] and Benin,[25] both in the southern geopolitical zone of Nigeria.

Nephrotic syndrome was seen more in older children, 10 years and above with a peak age 11-12 years in our study. This was similar to earlier studies from Ghana,[26] Pakistan,[27] and USA.[28] But studies from Port-Harcourt,[16] Enugu[29] and Kano[30] showed lower peak age of less than 8years. There was a male preponderance in this series. Similar reports were obtained in other studies within and outside the Nigeria,[6,26,27,29] but different from findings in Port Harcourt (Nigeria)[16] and a recent study from the USA,[28] in which there was equal gender distribution.

Oedema is the commonest presentation of NS in this study. Commonly affected site is the face, followed by abdomen, legs and was generalised (involving the scrotum) in half of the patients. This is in keeping with previous studies.[6,7,15-18,20,26,29,30] It results from the heavy proteinuria leading to reduction in plasma oncotic pressure with increased capillary ultrafiltration or as a consequence of an increased primary intra-renal renal avidity for sodium and water due to resistance to atrial natriuretic peptide and activation of epithelial sodium channels in the renal medullary collecting ducts.[6,31,32] Oedema may require symptomatic treatment. In this series most of our patients received diuretics like furosemide, hydrochlorothiazide, spironolactone and pooled plasma. Hypertension was seen in about 10% of our patients especially those with chronic kidney disease (CKD). This was lower compared to earlier studies.[16,18,28,29] The presence of hypertension on initial diagnosis could therefore be a strong pointer to a higher possibility of a non-minimal change type of nephrotic syndrome possibly steroid resistant nephrotic syndrome.[33] Other atypical presentations seen in our series include: haematuria, fever and cough

Features of complications like headache and convulsion were not seen in our series. Also, secondary nephrotic syndrome (SNS) was identified in our study and includes Sickle cell anaemia (HbSS) with Nephrotic Syndrome, HIV Associated Nephropathy, Disseminated Tuberculosis and Post-infectious Glomerulonephritis.

Steroid sensitive nephrotic syndrome (SSNS) was seen in 73.3%. This high value is in keeping with studies from Enugu,[34] Ibadan[17] and Abuja.[6] Our study may be highlighting a crop of Black children with NS having increasing sensitivity to steroid even at an older age. The finding of high steroid sensitivity in this study may also be due to low

record of atypical features of NS including hypertension (10.0%), and haematuria (10.0%).
Steroid resistant nephrotic syndrome (SRNS) was reported in 16.7% of the children in this study. This is similar to results obtained in some recent studies in our environment [6,16-18,26,34,35] This is in contrast to previous reports where researchers had found a higher prevalence of SRNS in black children with nephrotic syndrome. [14,30] These findings demonstrate that genetic, ethnic and geographic factors may influence the epidemiology of childhood NS. Also, three of our patients with SRNS progressed to chronic renal disease (CKD) with two in End-Stage Renal Disease (ESRD) and required dialysis and renal biopsy; they were lost to follow-up due to the high cost of treatment.

The rate of frequent relapse nephrotic syndrome (FRNS) in this study was 10.0%. This is low compared to that reported in Port Harcourt, Nigeria [6] and Ghana.[26] FRNS in this study was seen in children greater than 9 years, however, 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). [6,36] The occurrence of steroid resistance and frequent relapse necessitate the use of steroid-sparing agents in order to maintain sustained remission, delay progression to end-stage renal disease and minimize steroid toxicity.[1,37] Cyclophosphamide had been the preferred first steroid-sparing agent to be introduced in management of FRNS or Steroid dependant NS developing steroid toxicity.[1,37] We used oral cyclophosphamide in this study. The other steroid-sparing drugs such as cyclosporine A, mycophenolate mofetil and tacrolimus [37] were unavailable in Calabar.
Most of our patients were discharged, only three left against medical advice mainly on account of financial constraint and none died. This outcome may be traced to most of them presenting early within 4 weeks of illness, hence, with lower incidence of complications. However, 29.6% were lost to follow-up. This is challenging as they may progress to CKD and ESRD.
In conclusion, oedema is the commonest presentation of nephrotic syndrome in Calabar with few atypical features like cough, fever, haematuria and hypertension. Most are SSNS with few SRNS and FRNS. Early presentation and prompt treatment enhanced our good outcome.

LIMITATION:

1. Inability to do kidney biopsy (due to financial constraint) especially for the SRNS and FRNS children to know the histological pattern

CONFLICT OF INTEREST: None

SOURCE OF FUNDING: Self

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