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Review Article

Clinical Profile of Children with Nephrotic Syndrome at a Tertiary Hospital in North Central Nigeria

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Abstract

Background/Objective: Nephrotic syndrome is an important disease of childhood.

Materials and Methods: This was an observational study describing the clinical profile of children with nephrotic syndrome at Dalhatu Araf Specialist Hospital.

Results: Seventeen children with idiopathic nephrotic syndrome participated in this study. The mean age was 8.4±3.6years. The male: female ratio was 1:1.83. Most of the children (82.4%) were from low socioeconomic class families. More females than males were hypertensive (P=0.013). Using the Fractional Excretion of Sodium (FeNa) cutoff of 0.2, 41.2% were under fill and overfill respectively. Volume status was undetermined in 17.6%. Severe oedema was found in 52.9% and reduced renal function in 41.2% of the children. Eleven (64.7%) children had steroid sensitive nephrotic syndrome while 23.5% had steroid resistant nephrotic syndrome. The default rate was 29.4%. Mortality was recorded in 3 (17.7%) children, two were SRNS while the third was SSNS. There was a significant association between steroid resistant nephrotic syndrome and hypertension (P=0.043), and between mortality and intravascular volume status (P=0.043).

Conclusion: Our study confirms an increasing trend of steroid responsiveness in African children with idiopathic nephrotic syndrome. We highlight the burden of severe oedema, reduced glomerular filtration rate, hypertension, high default rates and low socio-economic class in children with nephrotic syndrome in our setting.

Keywords: Nephrotic syndrome; Oedema; Steroid; Underfill; Overfill

Abbreviations

FeNa: Fractional Excretion of Sodium; AKI: Acute Kidney Injury; UPCR: Urine Protein Creatinine Ratio; BP: Blood Pressure; HIV: Human Immunodeficiency Virus; CCF: Congestive Cardiac Failure; ESR: Erythrocyte Sedimentation Rate; UTI: Urinary Tract Infection; CR: Complete Remission; PR: Partial Remission; LR: Late Remission; INS: Idiopathic Nephrotic Syndrome; SDNS: Steroid Dependent Nephrotic Syndrome; FRNS: Frequent Relapsing Nephrotic Syndrome; NFRNS: Non Frequent Relapsing Nephrotic Syndrome; SSRNS: Secondary Steroid Resistant Nephrotic Syndrome; SRNS: Steroid Resistant Nephrotic Syndrome; SD: Standard Deviation; SPSS: Statistical Product and Service Solutions; RAASi: Renin Angiotensin Aldosterone System Inhibitors; RAAS: Renin Angiotensin Aldosterone System; IPNA: International Paediatric Nephrology Association; MFR: Male Female Ratio; eGFR: Estimated Glomerular Filtration rate; Hb: Hemoglobin; Spp: Species; MCD: Minimal Change Disease; FSGS: Focal Segmental Glomerulosclerosis; TTKG: Transtubular Potassium Gradient; ESRD: End Stage Renal Disease.

Introduction

The incidence of Nephrotic syndrome varies with age, race and geography [1]. In western countries, in children less than 16 years old the annual incidence of nephrotic syndrome is 1-3 per 100000 children, while the incidence of nephrotic syndrome in African countries ranges between 4.6 cases to 13 cases per annum [1-4]. Nephrotic syndrome has a male predominance with a Male to Female ratio of 2:1 in the first decade. Oedema is a common presenting complaint in children with nephrotic syndrome. It results from the heavy proteinuria and a consequent 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 [3,5-7]. Oedema may be severe and require symptomatic treatment. Treatment of oedema is highly determined by the intravascular volume. This has led to the classification of the child with nephrotic syndrome and decreased intravascular volume as being underfill while nephrotic syndrome with euvolaemia or increased intravascular volume is overfill. Differentiating between the severely oedematous child with underfill from those with overfill state using clinical parameters alone is difficult and misleading [5-9]. Laboratory parameters are more effective in differentiating between the underfill and overfill. Children with nephrotic syndrome are described as underfill if Fractional Excretion of Sodium (FeNa) is <0.2 while children with FeNa of ≥0.2 are overfill [8-10]. This distinction between underfill and overfill helps the clinician decide on treatment of severe oedema when present. Diuretics alone can be safely used in the overfill child while the use of

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diuretics alone will cause intravascular hypovolemia, Acute Kidney Injury (AKI) and thrombosis in the underfill child [9].

Previously, steroid sensitive nephrotic syndrome was described as the predominant type seen in 80% of idiopathic nephrotic syndrome in western countries while steroid resistant nephrotic syndrome was more prevalent among black or African children [11-14]. A changing epidemiology has however been reported in recent times with an increasing incidence of steroid sensitive nephrotic syndrome reported from recent studies in Nigeria [4, 15-18].

The advances in the understanding of nephrotic syndrome, the changing epidemiology and regional differences in disease pattern, necessitates further studies on clinical types of nephrotic syndrome, management pattern and determination of trends across various settings. Our study reports on the demographic, clinical, therapeutic profile, complications and outcomes of children with nephrotic syndrome seen at a tertiary health centre in Lafia, north central Nigeria. This will be the first study of its kind carried out in Lafia, Nigeria.

Materials and Methods

This was a prospective observational study conducted at the renal unit of the paediatrics department of Dalhatu Araf Specialist Hospital Lafia, a tertiary hospital in north central Nigeria from April 2019 to March 2020. The Ethics and Research Committee of Dalhatu Araf Specialist Hospital gave ethical approval for this study. Consent to participate and publish was obtained from the parents/care givers. All the children with nephrotic syndrome seen during the year in review were recruited into our study. Diagnosis of nephrotic syndrome was made in those children with heavy proteinuria either by demonstrating a urine protein $\geq 3^+$ on urine dipsticks or early morning spot Urine Protein Creatinine Ratio (UPCR) >2mg/mg, with hypoalbuminaemia <25g/L, hypercholesterolaemia >5.2mmol/l, and generalized oedema [1,19].

Measurements

Parameters including gender, presenting symptoms, past medical history, drug history, family history of renal disease, family socio-economic class using the Olusanya socio-economic class classification system [20] co-morbid disease at time of diagnosis, complications. Presentation with severe oedema, history of use of diuretics before presentation, treatment for severe oedema. Examination findings with careful attention to oedema and volume status including pulse volume, Blood Pressure (BP) and capillary refill, weight, height, height for age centiles were all documented. Investigations carried out included urine dipsticks utilizing the sulfosalicylic acid method using Combi-11 dipsticks, paired serum and urine electrolytes, lipid profile, serum albumin, serum calcium and complete blood count with erythrocyte sedimentation rate. A mantoux test, chest radiograph to rule out tuberculosis, and viral screening for hepatitis B and C and Human Immunodeficiency Virus (HIV) were all carried out. Fractional Excretion of Sodium (FeNa) was calculated for all children on spot urine using the formula FeNa= (urine sodium x serum creatinine (mg/dl)/plasma sodium x urine creatinine (mg/dl) [9,21,22]. Children with specific complications were managed accordingly.

Definitions: For the purpose of this study:

A child was classified as a *defaulter* if at least 2 clinic visits were missed during the follow up period.

Underfill was defined as fractional excretion of sodium <0.2% and Overfill was defined as FeNa of ≥0.2.22. For children who had been treated with diuretic (frusemide) before presentation, fractional excretion of sodium was not used in determining intravascular volume status [22].

Severe oedema was defined as presence of

1. Marked eyelid oedema limiting eye opening and compromising vision.

2. Tense ascites with abdominal compartment syndrome.

3. Massive pericardial or pleural effusions, severe scrotal or labial oedema, pulmonary oedema, Congestive Cardiac Failure (CCF), volume related hypertension.

4. Increased skin tension with skin breakdown and skin exudation.

5. Pre-renal crisis with oliguria (incipient AKI) [22,23].

Severe oedema, tuberculosis, acute kidney injury requiring dialysis, seizures from hypertension, bacterial peritonitis with or without confirmatory cultures, septicaemia, shock, stroke, tuberculosis with or without acid fast bacilli demonstration in tissue samples, chronic kidney disease, end stage renal disease, cardiac failure, pulmonary oedema were considered *serious complications*. Non-severe oedema, asymptomatic electrolyte abnormalities, asymptomatic hypertension, conjunctivitis, otitis media, urinary tract infections were considered *non-serious complications*. Tuberculosis was considered in children with hilar lymphadenopathy on chest radiograph, in the presence of peripheral blood lymphocytosis. The additional presence of elevated Erythrocyte Sedimentation Rate (ESR), positive mantoux test and isolation of mycobacterium on geneXpert also strengthened the consideration of tuberculosis. Urinary Tract Infection (UTI) was defined by isolation of bacterial isolate on urine culture.

Hypertension was defined as BP >95th centile for age, gender and height. Socioeconomic class was determined using the Olusanya socio-economic indices, which employed the use of father's occupation and mother's educational level [20]. Complete Remission (CR) was defined as urine protein nil or trace on 3 consecutive days urine dipsticks or UPCR of <0.2mg/mg [22, 24]. Relapse was defined as urine protein 2^+ or more with or without oedema for 3 consecutive days or urine protein 3^+ to 4^+ with oedema in a child who was previously in remission [24]. Partial Remission (PR) was defined as a urine protein level of 1^+ or 2^+ by dipsticks for 3 consecutive days [24,25]. Late Responder (LR) was defined as complete remission attained by 6 weeks of daily prednisolone at 2mg/kg/d [22].

Idiopathic Nephrotic Syndrome (INS) was defined as nephrotic syndrome in the absence of secondary causes or systemic disease mediated glomerular disease. Steroid Sensitive Nephrotic Syndrome (SSNS) was defined as complete remission with use of prednisolone at 2mg/kg/d at any point during the first 4 weeks of treatment or a history of such in patients who were not first presenters [24]. Steroid Dependent Nephrotic Syndrome (SDNS) was defined as relapsing whilst on prednisolone therapy or within 14 days of discontinuation of steroid therapy [24]. Frequently Relapsing Nephrotic Syndrome

(FRNS) was defined as 2 or more relapses within the first 6 months of presentation or 4 or more relapses in any 12 months [24]. Non-Frequent Relapsing Nephrotic Syndrome (NFRNS) was defined as relapse 2 to 3 times in a 12-month period [24].

Steroid Resistant Nephrotic Syndrome (SRNS) was defined as absence of remission in spite of daily prednisolone regimen of 2mg/kg/day for 4 weeks [24]. Secondary Steroid Resistant Nephrotic Syndrome (SSRNS) was described as development of resistance in a child who had previously been steroid sensitive [24]. Confirmatory period was defined as the period between 4 to 6 weeks of using the standard high dose oral prednisolone at 2mg/kg/d, to assess the response of further treatment with prednisolone and initiate Renin-Angiotensin-Aldosterone System Inhibitors (RAASi) [22]. Stunting was defined as height centile <5 thcentile or more than 2 Standard Deviation (SD) below world health organization child growth standards median.

Statistical analysis

Data was analyzed with the Statistical Product and Service Solutions (SPSS) version 16. Qualitative variables presented using frequency tables and percentages. Quantitative variables were presented using means and standard deviations and compared with T-test. Descriptive statistics including chi-square tests, fishers exact test when appropriate. *P* value less than 0.05 was considered significant.

Treatment regimen: The regimen used for treatment of nephrotic syndrome in our hospital involved use of oral prednisolone at 2mg/kg/d (maximum of 60mg) as a single morning dose for 6 weeks reduced to every alternate day for another 4 weeks subsequently weaned off over a 2 week period.

For relapse, prednisolone was given at 2mg/kg/d as a single morning dose till complete remission was attained followed up with alternate day dosing for 4 weeks subsequently weaned off over 2 weeks.

The children with SDNS or FRNS were first treated by re-inducing remission with prednisolone then maintaining on low dose prednisolone on alternate day at doses between 0.5mg/kg to 0.7mg/kg as tolerated on alternate day for 6 months if no further relapses. Any further relapses were treated with second line drugs including levamisole 2.5mg/kg on alternate day for a year, or chlorambucil 0.2mg/kg/d as single daily dose for 2 months. For the steroid resistant nephrotic syndrome child after four to six weeks on 2mg/kg/d of prednisone, RAASi, and cyclosporine were commenced and prednisolone weaned off. All children on high dose oral prednisolone were also treated with omeprazole and calcium carbonate with vitamin D3 for gastroprotection and osteoporosis prevention respectively.

Severe oedema in underfill nephrotic syndrome children was treated with intravenous (IV) 20% Albumin 5ml/kg over 4 hours with IV frusemide 2mg/kg mid-way through the IV 20% albumin infusion if the parents could afford to procure albumin or with trial of IV 20% mannitol 5ml/kg infusion with frusemide 2mg/kg midway or after the mannitol infusion if the parents were unable to afford albumin infusion. For those underfill children with severe oedema who were given a trial of IV 20% Mannitol-frusemide combination, IV 20% albumin with frusemide was used if there was poor response to the trial of IV 20% Mannitol-frusemide combination. Diuretics alone were not used in the treatment of severe oedema in underfill children [22]. Prompt response was defined as brisk diuresis; increasing urine output and weight drop with resolution of oedema within 3 to 4 days of commencing IV 20% mannitol or IV 20% Albumin infusion.

Severe oedema in the overfill child was treated with diuretics alone (frusemide) [22]. Intravenous 20% albumin and 20% Mannitol were not used in overfill children. Albumin infusion was also used for children with symptomatic hypovolemia and or incipient AKI [22].

The calcium channel blocker amlodipine was used to treat hypertension. For children with SRNS, angiotensin converting enzyme inhibitor (lisinopril/Ramipril) was used in the confirmatory period of treatment in accordance with Trautmann et al., International Paediatric Nephrology Association (IPNA) clinical practice recommendations [22]. The option of renal biopsy was offered to all steroid resistant children and to children with FRNS in whom further immunosuppression was being considered. Genetic testing was not possible in our setting.

Results

Seventeen children with nephrotic syndrome were seen during the year in review. The children were between 4 to 16 years old with the mean age at presentation of 8.4±3.6years. Most (64.7%) of the children were age 5 to 10 years old. There were more females than males with an M: F ratio of 1:1.83. All the children above 10 years old were female, females also predominated in the 5 to 10 year age group while an equal gender distribution was found in the children <5 years old (Table 1).

Presentation and relapses

Eleven of the children (64.7%) were first time presentations, the remaining 35.3% children were not first time presentations. Of the 17 children, 23.5% never relapsed during the year in review, 11.7% were FRNS, and 5.9% had a non-frequent relapsing nephrotic syndrome.

Socioeconomic class and nutritional status

Most (82.4%) of the children were from low socioeconomic class families, 17.3% were middle socioeconomic class in addition, no child was from the upper socio-economic class.

Steroid response and intravascular volume status

All the children seen had Idiopathic Nephrotic Syndrome (INS). Steroid sensitive nephrotic syndrome was seen in 11 (64.7%) of the 17 children, two children (11.8%) had FRNS, one child (5.9%) had SDNS and four (23.5%) had SRNS. Steroid responsiveness was undetermined in two children (11.8%) children who had defaulted before their steroid sensitivity could be determined (Table 2).

There was no significant difference between the males and the

Table 1: Age and gender distribution of study participants.

Age (years)	Male Freq (%)	Female Freq (%)	Total	X^2 *P*-value
<5	1 (16.7)	1 (9.1)	2 (11.8)	
5-10	5 (83.3)	6 (54.5)	11 (64.7)	
>10	0 (0.0)	4 (36.4)	4 (23.5)	
Total	6 (35.3)	11 (64.7)	17 (100.0)	0.126
Mean Age	6.67±1.6	9.36±4.1	8.4±3.6	T=1.543 (0.144)

X^2 =Chi-square Freq=Frequency %=percentage T=T-test

Table 2: Demographic, clinical characteristics and steroid response of the 17 study participants.

Characteristics	Male	Female	Total	X^2 *p*-value
Social class				>0.999
Low	5 (83.3)	9 (81.8)	14 (82.4)	
Middle	1 (16.7)	2 (18.2)	3 (17.3)	
High	0 (0.0)	0 (0.0)	0 (0.0)	
Past history				0.333
First presentation	5 (83.3)	6 (54.5)	11 (64.7)	
Not first presentation	1 (16.7)	5 (45.5)	6 (35.3)	
Steroid response				0.182
SSNS	5 (83.3)	6	11	
SDNS	1 (16.7)	0	-1	
FRNS	0	-2	-2	
SRNS	1	3	4	
Undetermined steroid response	0	2	2	
Intravascular volume status				0.288
Underfill	4 (66.6)	3 (27.3)	7 (41.2)	
Overfill	1 (16.7)	6 (54.5)	7 (41.2)	
Undetermined volume status (received frusemide)	1 (16.7)	2 (18.2)	3 (17.3)	
Serious complications	5	9	14	
Family type				0.116
Monogamous	1 (16.7)	5 (45.5)	6 (35.3)	
Polygamous	5 (83.3)	4 (36.3)	9 (52.9)	
Divorced	0 (0.0)	0 (0.0)	0 (0.0)	
Widowed	0 (0.0)	2 (18.2)	2 (11.8)	
Separated	0 (0.0)	0 (0.0)	0 (0.0)	
Mean number of children in family	7.5	6.2	6.64	

X^2 = Chi-square

Table 3: Mean clinical and laboratory values among the study participants between genders.

Variable	Male	Female	Total	T-test	*P*-Value
Systolic BP	103.3±17.5	133.8±26.8	123±27.8/	2.823	0.013
Diastolic BP	71.7±20.4	92.2±26.7	84.9±26.0	1.771	0.1
UPCR (mg/mg)	2.0±0.7	2.65±0.8	2.42±0.8	1.672	0.122
eGFR (ml/min/1.73m^2)	100.4	79.59	86.93±50.5	0.901	0.383
HB (g/L)	10.2±1.62	9.8±2.5	9.9±2.2	0.378	0.711
BMI	18.14±4.4	17.11±1.0	17.47±2.6	0.764	0.457
Sodium (mmol/L)	138±5.1	142.2±8.5	140.7±7.6	1.271	0.223
Potassium (mmol/L)	4.15±0.8	3.9±0.8	4.0±0.8	0.689	0.505
Albumin (g/L)	14.5±4.2	15.0±4.0	14.8±3.9	0.238	0.817
Cholesterol (mmol/L)	10.65±4.5	9.0±2.6	9.6±3.3	0.831	0.434
Calcium (mmol/L)	2.6±0.4	2.45±0.3	2.4	0.802	0.393
ESR (mm/hr)	108.8±17.3	104.4±23.0	105.9±20.7	0.452	0.659

T-test=Student T test

females with respect to social class (P=>0.999), steroid response (P=0.182), intravascular volume status (P=0.288) and family type (P=0.116) (Table 2).

The female children had higher systolic blood pressures compared to male children. This difference was statistically significant P=0.013. The difference in diastolic blood pressures between male and female children was not statistically significant P=0.100.

Although the female children had higher mean UPCR (P=0.122), mean sodium (P=0.223), and mean albumin (P=0.817) compared to the male children, the differences were not statistically significant. Though not statistically significant, male children had higher mean Estimated Glomerular Filtration Rate (eGFR) (P=0.383), mean Hemoglobin (Hb) (P=0.711), mean potassium (P=0.505), mean cholesterol (P=0.434), mean calcium (P=0.393) and mean ESR (P= 0.659) (Table 3).

All the children with SRNS were hypertensive compared with 36.4% of the children with SSNS who were hypertensive. This difference was statistically significant (P=0.043). The difference with respect to SSNS and SRNS when relating to gender (P=0.299), social class (P=0.633), presence of typical and atypical features (P=0.390), severity of oedema (P=0.137), presence of infections (P=0.654) and reduced eGFR (P=0.170) were all not statistically significant (Table 4). All the laboratory parameters (except mean UPCR, mean sodium and mean cholesterol) were lower in the SRNS children. No significant difference was demonstrated (Table 5).

Table 4: Associations between clinical parameters and steroid responsiveness.

Variables	SSNS	SRNS	Unknown response status	X^2 *p*-value
Age (mean)	7.55±3.2 years	8.75±4.6 years	12.5±0.7	T=1.799±0.202
Age group				
<5 10-May >10	1 (9.1) 9 (81.8) 1 (9.1)	1 (25.0) 2 (50.0) 1 (25.0)	0 (0.0) 0 (0.0) 2 (100.0)	
Gender				0.299
Male Female	5 (45.5) 6 (54.5)	1 (25.0) 3 (75.0)	0 (0.0) 2 (100)	
Socioeconomic class				0.633
Low Medium	9 (81.8) 2 (18.2)	3 (75.0) 1 (25.0)	2 (100.0) 0 (0.0)	
Features				
Typical features	9 (81.8)	0 (0.0)	0 (0.0)	0.39
Atypical features	2 (18.2)	4 (100.0)	2 (100.0)	
Hypertension Age Microscopic haematuria Low eGFR	3 1 8 4	4 1 2 2	2 2 1 2	
Presence of Oedema				0.639
Yes No	10 (90.9) 1 (9.1)	4 (100.0) 0 (0.0)	2 (100.0) 0 (0.0)	
Presence of severe Oedema				0.137
Yes No	6 4	3 (75.0) 1 (25.0)	0 (0.0) 2 (100)	
Hypertension				0.043
Yes No	4 (36.4) 7 (63.6)	4 (100.0) 0 (0.0)	1 (50.0) 1 (50.0)	
Anaemia				0.238
Yes No	3 (27.3) 8 (62.7)	3 (75.0) 1 (25.0)	1 (50.0) 1 (50.0)	
Infections				0.654
Yes No	9 (81.8) 2 (18.2)	3 (75.0) 1 (25.0)	1 (50.0) 1 (50.0)	
Reduced eGFR				0.17
Yes No	4 (36.3) 7 (63.7)	2 (50.0) 2 (50.0)	2 (100.0) 0 (0.0)	
Mean GFR	96.7	88.3	30.5	
AKI	0	0	1	
Underfill	6	1	0	
Overfill	4	2	1	

X^2=Chi-square T-test=Student T test

Serious complications

Serious complications were documented in 82.4% of the children.

Severe oedema

Severe oedema was seen in nine (52.9%) of the children, six (35.2%) were SSNS and three (17.7%) were SRNS. Of the six children with SSNS and severe oedema, four were underfill, one was overfill and last child had an undetermined intravascular volume status on account of prior use of frusemide. Two of the underfill SSNS children responded with brisk diuresis to IV mannitol-frusemide combination while the other two responded only to IV albumin-frusemide after an initial poor response to IV mannitol-frusemide combination treatment (Table 4).

Of the three children with SRNS and severe oedema. The first child was underfill, responded poorly to IV Mannitol-frusemide trial, and then achieved brisk diuresis with IV Albumin-frusemide combination therapy. The second child was overfill and received only frusemide. The third had an undetermined volume status also due to prior use of frusemide (Table 4).

Reduced renal function

Renal function was determined in all the children by estimating the glomerular filtration rate using the bedside Schwartz formula. Eight (47.1%) of the 17 children had reduced renal function. The mean eGFR was 86.93ml/min/1.73m^2.The eGFR though not statistically significant was found to be lower among female children (mean 79.59ml/min/1.73m^2) than male children (mean 100.4ml/min/1.73m^2) and also lower among children with SRNS (88.3ml/min/1.73m^2) than children with SSNS (96.69ml/min/1.73m^2) (Table 4,5).

Table 5: Associations between laboratory parameters and steroid responsiveness.

Variables	SSNS	SRNS	Unknown steroid response status	F-test *p*-value
UPCR	2.19±0.8	2.8±1.0	2.95±0.2	1.269 (0.311)
GFR	96.7±55.1	88.5±26.0	30.7±33.5	1.546 (0.247)
HB	10.3±2.4	9.2±1.7	9.3±2.2	0.416 (0.667)
Sodium	139.0±7.5	145.3±7.4	140.7±7.6	1.008 (0.390)
Potassium	4.0±0.8	3.6±0.4	4.4±1.6	0.661 (0.532)
Albumin	14.9±3.5	12.5±4.8	19.0±1.4	2.063 (0.164)
Cholesterol	9.86±3.5	10.15±3.5	6.9±1.6	0.723 (0.503)
corrected calcium	2.54±0.33	1.75±0.44	2.27±0.04	0.512 (0.610)
ESR	105.9±13.1	96.5±30.5	125±35.4	1.316 (0.299)
Hypoalbuminaemia				
Yes	11 (100.0)	4 (100.0)	2 (100.0)	1
No	0 (0.0)	0 (0.0)	0 (0.0)	
Hypercholesterolaemia				
Yes	11 (100.0)	4 (100.0)	2 (100.0)	1
No	0 (0.0)	0 (0.0)	0 (0.0)	
Hyponatraemia				
Yes	2 (18.2)	0 (0.0)	0 (0.0)	0.39
No	9 (81.8)	4 (100.0)	2 (100.0)	
Hypokalemia				
Yes	2 (18.2)	0 (0.0)	1 (50.0)	0.267
No	9 (81.8)	4 (100.0)	1 (50.0)	

F Test=F Statistics Test

Two children (11.8%) had hypertensive encephalopathy, four (23.5%) had tuberculosis, one child (5.9%) had CCF and pulmonary oedema, two children (11.8%) had presumed pulmonary embolism, another two (11.8%) had severe anaemia requiring blood transfusion, one child (5.9%) each had spontaneous bacterial peritonitis and sepsis during the period in review.

Non-serious complications. Asymptomatic hypertension was seen in seven children (41.2%), six children (35.3%) had UTI, one child (5.9%) each had otitis media, bronchopneumonia and conjunctivitis.

Laboratory Results

Among the six children with UTI, klebsiella specie (spp.) was the most common (66.7%) organism cultured, escherichia coli (16.7%) and staphylococcus aureus (16.7%) were the other uropathogens cultured. There were no mixed growths on urine culture. All the children had urine protein 3^+ to 4^+ on urine dipsticks using the sulfosalicylic acid method and mean spot urine protein creatinine ratio was 2.42 mg/mg. All the children had hypoalbuminaemia, and hypercholesterolaemia. The FRNS child who had renal biopsy showed a minimal change nephrotic syndrome histology. None of the 4 SRNS had renal biopsy done or genetic testing done. This was due to financial constraints.

Treatment

SSNS: Eleven (64.7%) of the children were steroid sensitive. The child with SDNS was treated with chlorambucil, attained complete remission within 3 weeks of starting chlorambucil. Remission was however not sustained. He was subsequently started on levamisole with maintenance alternate day prednisone and attained sustained remission. The two children with FRNS are also on alternate day levamisole with maintenance alternate day prednisone.

SRNS: Of the 4 children with SRNS, only one child was managed beyond confirmatory period of treatment. The child was treated with cyclosporine for 9 months, angiotensin converting enzyme inhibitor (lisinopril) and attained partial remission within 6 months. She subsequently had frequent relapses on cyclosporine in the latter 3 months of cyclosporine therapy. Cyclosporine was discontinued after 9 months and she was subsequently tried on the alkylating agent chlorambucil for two months. She achieved partial remission subsequently. She is now on maintenance Lisinopril and low dose alternate day maintenance prednisone, her last urine dipsticks showed 1^+ protein.

Outcome

Five children (29.4%) defaulted in the period of this study. Three children (17.7%) died. Of the three children, 2 were SRNS and one was SSNS. The SSNS child had previously defaulted and re-presented in the study period with end stage renal disease.

Of the three children that died, two of them had undetermined intravascular volume status (using FeNa) due to the fact that they had received frusemide prior to presentation. A significant association was found between volume status and mortality (P=0.043) (Table 6). No significant association was found between the default rate and low socioeconomic class P=0.515 (Table 7). No significant association

Table 6: Associations between intravascular volume status and mortality.

Characteristics	Died		Total	X^2 *p*-value
	Yes	No		
Overfill	1 (14.3)	6 (85.7)	7 (41.2)	
Underfill	0 (0.0)	7 (100.0)	7 (41.2)	
Undetermined	2 (66.7)	1 (7.1)	3 (17.6)	
Total	3 (17.6)	14 (82.4)	17 (100.0)	0.043*

X^2=Chi-square

Table 7: Association between social class and defaulting from treatment and follow up.

Defaulted	Social class		Total	*X2 p*-value
	Low	Middle		
Yes No	5 (100.0) 9 (75.0)	0 (0.0) 3 (25.0)	5 (29.4) 12 (70.6)	
Total	14 (82.4)	3 (17.6)	17 (100.0)	0.515

X^2=Chi-square

Table 8: Association between steroid response and mortality.

Characteristics	Died		Total	X^2 *p*-value
	Yes	No		
SRNS	2 (21.4)	2 (33.3)	4 (23.5)	
SSNS	1 (9.1)	10 (90.9)	11 (64.7)	
Undetermined	0 (0.0)	2 (100.0)	2 (11.8)	
Total	3 (17.6)	14 (82.4)	17 (100.0)	0.166

X^2=Chi-square

was found between steroid responsiveness and mortality (P=0.166) (Table 8).

Discussion

The mean age in this study was 8.4 years. This is similar to reports by other researchers [3,4,14,26,27] but contrary to other reports of nephrotic syndrome being primarily a disease seen in the pre-school age group [18,28]. In our study, age 5 to 10 years was the highest peak age of nephrotic syndrome. This is in contrast to reports [17,18]. Who reported peak age of <5 years but similar to the report [2,15,26]. Our study shows a female predominance across age groups 5-10 years and among adolescents. This is in stark contrast to the common description of a male predominance across all ages in previous studies [1,2,3,14,18,29-34]. All the adolescents in this study were females. Our finding is also in contrast to reports of an equal gender affectation among adolescents [1,2,3,14,18,29-34]. To the best of our knowledge, this study is the only study where a female preponderance was reported among children with nephrotic syndrome including adolescents. We do not have a plausible explanation for this. It is however clear that there is a wide variation in the epidemiology of nephrotic syndrome from region to region and from center to center. The age and gender distribution described thus far in our study emphasizes the regional differences in childhood nephrotic syndrome and highlights the necessity for further studies that describe changing trends over time and the possible environmental influence on the epidemiology of nephrotic syndrome.

Over eighty-two percent of the children in our study were from low socio-economic class families. This is similar to the reports [17,35] not surprising considering the fact that Nigeria and Ghana are lower middle income countries and that over 40% of Nigerians live on less than a dollar a day [36]. Although not replicated in our study, [17,35] reported a significant association between low socio economic class and the proportion of children with nephrotic syndrome while [37] found that low socioeconomic class increased the risk of relapse in childhood nephrotic syndrome. They however acknowledged the role of other factors in these associations [17].

They postulated a role for infection as an explanation for the higher number of nephrotic syndrome patients coming from low socioeconomic [17]. They were however unable to demonstrate this in their study. Our study on the other hand reports that 82.4% were from low socioeconomic class families and 76.5% of the children with nephrotic syndrome had presented with some form of infection. Perhaps an exploration of this theory using larger sample sizes of the nephrotic syndrome cohort may give more insight. This study reported a high default rate of 29.4% during the study period. All the children who had defaulted were from low socioeconomic class families. Low socioeconomic class has been reported to have a direct and clear relationship to compliance to treatment and follow up especially for chronic illnesses [38]. We however did not find a significant association between low socioeconomic class and the defaulters P=0.515. A high steroid response of 64.7% was found in our study. An increasing steroid sensitivity has been reported in recent studies carried out among African children [3,4,16-18,35]. The increasing steroid sensitivity has been attributed to the younger ages of the children in some of these studies [17,18]. This was not the case in our study where the mean age of the children was 8.4 years and most of the SSNS children were between 5 to 10 years old. The fact that the peak age in our study is high is against the previous theories of increasing sensitivity being due to younger ages of the children with nephrotic syndrome [17]. They also likened the increasing steroid sensitivities to the absence of secondary causes in their study [17]. In our study, we also found no secondary cause. Other West African studies report increased steroid responsiveness and also report a low prevalence of secondary causes [3,18,35]. Therefore, the theory of a link between increasing steroid sensitivity and a reduction or absence of secondary causes may be plausible. Further studies will need to be carried out to confirm this theory.

Renal biopsy with the aim of determining the histological types as part of the evaluation process of black children with nephrotic syndrome has been recommended by a few researchers [3,17]. This was on account of the increasing steroid responsiveness currently being seen in black children [3,4,16,18]. However, most centres carry out kidney biopsies only for the SRNS, FRNS and for presence of atypical features. Renal biopsies in SSNS children will be a tough sell especially considering the financial ramifications and risks associated with the procedure. Only 5.9% of the children in this study, (a child with FRNS) could afford to have a kidney biopsy carried out, and a minimal change histology pattern was found. This is not surprising, as it has been found that as much as 90% of children with Minimal Change Disease (MCD) are found to be steroid sensitive [24]. This may suggest that the increasing rate of steroid sensitivity may be because of a preponderance of minimal change disease histologic pattern. More studies will need to be carried out to either prove or disprove this theory.

Steroid resistant nephrotic syndrome was reported in 23.5% of the children in our study similar to the reports by [3,17,18,39]. This is in contrast to previous reports where researchers had found a higher prevalence of SRNS in black children with nephrotic syndrome [11-14] The above Nigerian studies have similar limitations of performing only minimal numbers of renal biopsies in the cohort of children with nephrotic syndrome [3,17,18]. However, all the aforementioned studies reported a predominant Focal Segmental Glomerulo Sclerosis (FSGS) pattern in the biopsied children with SRNS [3,17,18]. In our study, none of the SRNS children had kidney biopsy done. We could not determine the underlying histology of the children with SRNS. Based on above stated previous findings, FSGS is the most commonly identified histological pattern in children with SRNS in Nigeria. Our study shows that female gender and SRNS was significantly associated with hypertension. Our finding is similar [35] who described higher blood pressures among females and SRNS children. Their finding was however not statistically significant. Our finding is in contrast to the report by [3] who reported significantly higher blood pressures among SSNS children compared to SRNS. Hypertensive nephrotic syndrome children are more likely to have FSGS histology and more likely to be SRNS [40,41]. Although no SRNS child was biopsied in our study the finding of hypertension among the SRNS children may suggest that they have an underlying FSGS histology.

Reduced eGFR was seen in eight (47.1%) of the children in our study, this is higher than the report [3,26]. The higher rates of reduced eGFR in this study may be explained by the high default rates found. These children did not receive any treatment during the period of default and this may have led to progression of the disease. It could also be because of the high underfill rates (41.2%) among children in our study. Furthermore, three children had used frusemide before presentation. Underfill states and frusemide are known to compromise intravascular volume and renal blood flow leading to reduction in eGFR [7-9]. The significant association found between volume status and mortality supports the fact that all oedematous children should have a critical evaluation of their intravascular volume status [22]. All the children with severe oedema and underfill in this study had either IV mannitol-frusemide combination or IV 20% Albumin and frusemide combination treatment. The children with severe oedema and overfill volume status had diuretics alone. Intravascular volume status using FeNa was not assessed in 3 of the 17 children due to the fact that they had used diuretics before presentation and frusemide is known to increase urine sodium wasting which will give a higher FeNa value and consequently a wrong interpretation of intravascular volume especially in the absence of clear clinical signs of volume contraction. Two of these children had died. One of whom had end stage renal disease and the other had clinical signs of volume contraction including oliguria, small volume pulse, capillary refill >3 seconds, GFR >75ml/min/1.73m^2, increased Transtubular Potassium Gradient (TTKG) of 7.7. He was also hypertensive. The hypertension was found in presence of all aforementioned features of volume contraction and was therefore considered to be because of vasoconstriction from hypovolaemia-induced enhancement of the Renin Angiotensin Aldosterone System (RAAS) and sympathetic activity [24]. He received IV albumin.

The mortality rate in our study was 17.7%. Two of the 3 deaths were SRNS children who died in the confirmatory period of treatment, due to presumed thromboembolic events. They both had sudden onset of difficulty in breathing and deteriorating consciousness prior to their deaths. They were both on Aspirin. Prophylactic anticoagulant had been prescribed but was not bought because of financial constraints. The appropriateness of use of prophylactic anticoagulants or antiplatelet drugs in the prevention of nephrotic syndrome associated thromboembolism is debatable. Most children do not develop thromboembolism. The use of prophylactic anticoagualants would be unnecessary in such children and could increase risk of development of anticoagulant-associated bleeds [10]. At risk, children may be identifiable by carrying out thrombophilia screening to determine presence, if any of prothrombotic conditions that predispose to thromboembolism in them [10]. Thrombophilia screening was not possible in our setting. The existing protocol in our hospital is therefore antiplatelet (aspirin) or anticoagulant (clexane) prophylaxis in children with risk factors for thromboembolism including fluid losses (diarrhea, vomiting), thrombocytosis, prolonged hospitalization ≥4 days with limited mobilization in the severely oedematous child. Financial constraints still however hamper this prophylactic measure. The 3rd child who died though SSNS had previously defaulted and represented in End Stage Renal Disease (ESRD), pulmonary oedema and CCF. The association between mortality and steroid responsiveness was not statistically significant.

Conclusion

The higher peak and mean ages of the children studied, the female preponderance, high steroid sensitivity, and absence of secondary causes confirms that there is a changing epidemiology of idiopathic childhood nephrotic syndrome. All children with severe oedema should have a critical assessment of their intravascular volume to guide choice of treatment plan for the oedema. A high burden of low socioeconomic status, infections, reduced eGFR, and high default rates was highlighted in this study.

Limitations

We were limited by our inability to carry out renal biopsies in most of the children with clear indications for renal biopsy and by our small sample size. Financial constraints grossly limited the treatment available for the children in our study.

Recommendations

All children with steroid resistant nephrotic syndrome and difficult to control oedema should be given prophylactic anticoagulants and INR monitored. Thrombophilia screening should also be carried out if possible. All children with nephrotic syndrome should have a critical assessment of intravascular volume status before symptomatic treatment of severe oedema. There should be some form health insurance for children from low socioeconomic class families who have chronic diseases, as nephrotic syndrome this will require political will from the government.

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