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Reversed Clinical and Morphologic Characteristics of Idiopathic Childhood Nephrotic Syndrome

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Abstract

Background and Aims: Minimal change disease (MCD) is uncommon in Nigeria; in the sixties and eighties quartan malaria nephropathy accounted for more than 80.0% of all cases of childhood nephrotic syndrome (CNS). There is paucity of current clinical and morphologic data on CNS. This study therefore determined the incidence and prevalence of CNS, pre-treatment glomerular pathology of idiopathic CNS (ICNS), renal and patient outcome in steroid sensitive ICNS.

Methods: A non-randomized prospective study of consecutive cases of Nigerian children with idiopathic nephrotic syndrome was conducted over a 9-year period.

Results: CNS accounted for 1.26% of pediatric admissions. Fifty-four of 78 (69.2%) nephrotic children had ICNS (incidence, 0.44/100000/year). Median NS onset age was 7.1 (2.5-14.0) years. Male: female ratio was 1.7. The histopathologic lesions were membranoproliferative glomerulonephritis (MPGN, 44.4%), focal segmental glomerulosclerosis (FSGS, 25.9%), MCD (18.5%), mesangial proliferative glomerulonephritis (7.4%) and membranous nephropathy (3.7%). Overall cumulative complete remission (CR) rate 4 to 8 weeks post prednisolone treatment was 49.6%. Twenty-two of 25 with CR were early steroid responders while 3 were late responders. Median time to CR was 12.0 (3.0 – 46.0) days. Thirty relapses occurred; median time to first relapse was 11.0 months. Cumulative five-year relapse-free rate was 26.6%. Five-year renal survival was 16.1%. All patients with CR were followed-up for 6-93 (median, 22.0) months.

Conclusions: Prevalence of non-MCD was very high with significant resistance to prednisolone; poor renal survival was due to high frequency of MPGN and FSGS. Pre-treatment renal biopsy is advocated in our kind of patients so that steroid-sparing agents can be started early.

Keywords: Non-Minimal Change Disease, Remission, Relapse

Introduction

In developing countries nephrotic syndrome (NS) is a very common renal disorder; compared to developed countries the incidence is 15 to 50-fold higher (1). The need to tame the nephrotoxic proteinuria especially with regards to the frequently relapsing NS (FRNS), steroid dependent NS (SDNS), and steroid resistant NS (SRNS) has generated remarkable

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treatment trials (2-4). Minimal change disease (MCD) is the commonest and the most steroid responsive of all the idiopathic childhood NS (ICNS) glomerular morphologic types in non-Africans (5-7). Relapses are, however, very frequent (72.5-97.0%) (8-10). Minimal change NS (MCNS) is uncommon in Africa (11-15) except in Arab African, Indian and white South African children (14, 16, 17). Only in three of the eleven biopsy-proven reports of ICNS from Africa was MCD the principal lesion (18-20). In the remaining eight reports, diffuse proliferative glomerulonephritis (21, 22), membranoproliferative glomerulonephritis (MPGN) (12, 15), focal segmental glomerulosclerosis (FSGS) (13, 14), membranous nephropathy (MN) (23), and mesangial proliferative glomerulonephritis (MesPGN) (24) predominate. This pattern casts doubt on the ability to give reasonable care to nephrotic black African children without pre-treatment renal biopsy to guide treatment very early. Waiting for the standard 4-8 weeks steroid therapy period to establish steroid resistance before considering renal biopsy and steroid-sparing agents may promote disease progression. This non-randomized prospective study determined the incidence and prevalence of childhood NS, pre-treatment glomerular pathology in ICNS, renal and patient outcome in steroid sensitive ICNS in Nigeria where earlier studies revealed quartan malaria nephropathy (QMN) and MPGN as highly prevalent histopathologic lesions (11, 12, 15).

Patients and Methods

A non-randomized prospective study of Nigerian children with steroid sensitive ICNS was conducted between June 2000 and June 2008. The patients were followed-up for varied time length of at least six months. Patients were recruited up till June 30, and followed till December 31, 2008. The unit provides renal healthcare services to 1,530,000 children in Osun state, southwestern Nigeria. NS diagnostic criteria were oedema, plasma albumin <25 g/L, and proteinuria ≥40 mg/m^2/hour or a urinary protein-creatinine ratio (UPCR) ≥ 200 mg/mmoL by quantitative assessment or 3+/4+ proteinuria by dipstick. Nephrotic proteinuria was classified mild (≥ 40-120 mg/m^2/hour or ≥200-299 mg/mmoL), moderate (121-201 mg/m^2/hour or 300-399 mg/mmoL) and severe (>201 mg/m^2/hour or ≥ 400 mg/mmoL). ICNS was diagnosed when no etiology was found. Ethical approval and parental/guardians' consent were obtained. The study conformed to the provisions of the revised Declaration of Helsinki, Edinburg, 2000.

Definitions

Complete remission (CR) denoted proteinuria <4 mg/m^2/hour or UPCR <20 mg/mmoL or 0/trace proteinuria by dipstick for three consecutive days following daily steroid treatment for at least 4 weeks. Sustained remission: no relapse for at least six months. Partial remission (PR): proteinuria level of 4-39 mg/m^2/hour or UPCR 20-199 mg/mmoL or 1+/2+ proteinuria by dipstick. Early and late steroid response referred to CR within and after four weeks of treatment, respectively. Relapse: recrudescence of proteinuria ≥40 mg/m^2/hour or UPCR ≥200 mg/mmoL or ≥2+ by dipstick for three consecutive days after an initial CR. Frequent relapse (FR): if two or more relapses occurred within six months of initial CR or four or more relapses within a 12-month period. Infrequent relapse (IF): occurrence of one relapse within six months or two relapses in twelve months. Steroid dependence (SD): occurrence of two consecutive relapses either while reducing the steroid dose or within 14 days of cessation of steroid. Primary steroid resistance (SR): no response to at least four weeks of daily prednisolone treatment. Secondary SR: patients had initial CR but later developed FR followed by SD before finally becoming resistant. Estimated glomerular filtration rate (eGFR) <80 mL/min/1.73m^2 indicated renal insufficiency and poor renal survival if persistent for at least six

months. Renal survival was good if eGFR was persistently ≥80 mL/min/1.73m^2 for six months or more. Standard definition of hypertension (HTN) was used (25).

Inclusion and exclusion criteria

All newly confirmed cases of ICNS aged 2-16 years were recruited. Secondary etiologies like diabetes mellitus, obesity, congenital cyanotic heart disease, Bee sting, sickle cell disease, Churg-Strauss syndrome, Henoch-Schonlein purpura, systemic lupus erythematosus and infections like malaria, syphilis, schistosomiasis, viral hepatitis B/C, filariasis and human immunodeficiency virus were excluded. Nephrotic chronic renal failure patients were also excluded.

Investigations

These included full blood counts, platelets, plasma and urinary biochemical evaluations and renal ultrasound. Definitive investigations excluded the secondary etiologies listed above. Significant microhematuria and pyuria were defined as urinary red blood cells (RBC) ≥ 5/high power field (HPF) and white blood cells (WBC) ≥ 10 /HPF, respectively. eGFR was determined using the Schwartz formular (26). Chronic kidney disease (CKD) was assessed and classified according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (27).

Pre-treatment percutaneous renal biopsies were performed. Tissue sections were 2-3 microns thick. Five or more glomeruli per renal tissue specimen were regarded as adequate for reporting (28). Histopathologic examinations were performed and the glomerular lesions defined along standard diagnostic light microscopy lines by a renal pathologist who was blinded to the clinical details. To avoid bias in the interpretation of clinical findings, the histopathology result for each child was not obtained until after at least four completed weeks of steroid therapy.

Treatment

To establish steroid responsiveness or resistance, each patient was initially treated with prednisolone, 60 mg/m^2/day (daily prednisolone) for 4-8 weeks followed by 40 mg/m^2/48 hours (alternate prednisolone) for another 4 weeks and stopping at 20 mg/m^2/48 hours for 4 weeks. Occasional relapses were treated with daily prednisolone until remission followed by alternate prednisolone that was tapered to stop at 10 mg/m^2/48 hours for 4 weeks. FRNS and SDNS were treated with daily prednisolone until remission followed by alternate prednisolone for 8 weeks and thereafter tapered to stop at 10 mg/m^2/48 hours for 1-2 years. They also received oral steroid sparing agents namely, cyclophosphamide and/ or lisinopril, valsartan or levamisole for 1-2 years following CR with prednisolone. Hypercholesterolemia was treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG–CoA) reductase inhibitor.

Follow-up and outcome

Patients were seen in the clinic every 1-3 months depending on distance. Clinic visit evaluations included weight, height, vital signs, oedema, ascites, and proteinuria. Routinely, parents checked the urines of their children for proteinuria using the dipstick twice weekly and kept the records. UPCR and eGFR were assessed initially at 3 months and six monthly thereafter. Outcome indices were CR, PR, SD, FR, IR, SR, relapse-free period, patient and renal survival, study exit by reasons of death or voluntary discharge, and lost to follow-up.

Statistics

The SPSS 15.0 statistical software package for Windows Evaluation Version (SPSS 2006 Inc.) was used for the analysis. Descriptive statistics used comprised mean, standard deviation (SD), median, percentages, and proportions. The comparative statistics were hazard ratio, confidence interval,

Table 1. Some demographic and baseline clinical characteristics of the patients (N= 54)

Demographic and baseline clinical characteristics	Results
Overall nephrotic syndrome (NS) incidence	0.64/100000/year
Overall NS prevalence	5.1/100000
Idiopathic NS incidence	0.44/100000/year
Idiopathic NS prevalence	3.53/100000
Median onset age, years	7.1 (2.5 – 14.0)
Median diagnosis age, years	8.0 (2.1 – 14.0)
Age below 5 years	15 (27.8%)
Age above 5 years	39 (72.2%)
Gender	
Male	34 (63.0%)
Female	20 (37.0%)
Male to female ratio	1.7: 1
Overall mean blood pressure (BP)	
Systolic BP, mmHg	107.2 ± 15.6 (70 – 150)
Diastolic BP, mmHg	70.4 ±15.1 (50 – 120)
Number with hypertension	18 (33.3%)
Systolic BP, mmHg	124.4 ± 12.0 (110 – 150)
Diastolic BP, mmHg	87.5 ± 13.0 (60 – 120)
Overall mean pulse rate, beats/minute	104.2 ± 15.6 (72 – 140)

regression analysis, correlation coefficient, Kaplan-Meier survival analysis, and the log-rank test. P value <0.05 was considered statistically significant.

Results

All patients

Seventy-eight of 6,200 (1.26%) pediatric admissions was diagnosed nephrotic syndrome. Fifty-four of 78 (69.2%) were ICNS while the rest were secondary NS. Demographic and clinical characteristics and some baseline laboratory features of the patients are shown in Tables 1 and 2, respectively. Non-MCD was the predominant morphologic lesion (81.5%) (Figure 1). Figure 2 shows the variation of the glomerular morphologic types with different pediatric age groups. Impact of the glomerular morphologic types on some clinico-laboratory features of NS is summarized in Table 3 while Figure 3 illustrates the different outcome levels of prednisolone treatment. Twenty-four of 25 (96.0%) patients that were primarily steroid resistant had non-MCD. Outcome in 4 of 54 ICNS patients was unknown because they failed to complete at least 4 weeks of prednisolone treatment; they were lost to follow-up.

Steroid sensitive nephrotic syndrome

Twenty-two of 25 patients with CR were early steroid responders while 3 were late responders (all MPGN). Median time to CR was 12.0 (3.0-46.0) days. The overall cumulative probability of CR after 4 to 8 weeks of prednisolone was 49.6% by Kaplan-

Table 2. Some baseline laboratory characteristics of the patients (n= 54)

Baseline laboratory characteristics	Results
Mean hematocrit, %	33 ± 6.3 (20 – 45)
Overall mean serum urea, mmol/L	6.0 ± 4.3 (2.3 – 24.9)
Number with azotemia	28 (52.0%)
Mean serum urea, mmol/L	11.1 ± 4.0 (6.6 – 24.9)
Overall mean eGFR, mL/min/173 m^2	96.8 ± 50.0 (27 – 286)
Number with reduced eGFR	25 (46.3%)
Mean eGFR, mL/min/173 m^2	59.2 ± 14.9 (27 – 78)
Mean total serum protein, g/L	47.3 ± 9.4 (13 – 75)
Mean total serum albumin, g/L	18.8 ± 4.0 (7 – 24)
Mean serum cholesterol, mmol/L	8.8 ± 3.5 (3.2 – 17.0)
Mean proteinuria (n= 49), mg/m^2/hour[a]	194.7 ± 153 (46 – 734)
Mild (≥ 40 – 120 mg/m^2/hour)	16 (32.7%)
Moderate (121–201mg/m^2/hour)	17 (34.7%)
Severe (>201mg/m^2/hour)	16 (32.7%)
Microhematuria (≥ 5 red blood cells/high power field)	17 (31.5%)
Hyaline casts	23 (42.6%)
Granular casts	10 (18.5%)
Tubulointerstitial (TI) score[b]	
Mild (0 – 2)	33 (61.2%)
Moderate (3 – 5)	19 (35.2%)
Severe (6 – 8)	2 (3.6%)

[a] Proteinuria was determined in 5 of 54 patients by urinary-protein creatinine ratio (269.0 – 2479.0 mg/mmoL)

[b] There was no correlation between remission and TI injury severity (r = +0.178; p = 0.197)

Meier survival analysis. MCD complete remission rate was 90.0% (Figure 4). The cumulative hazard of CR was 2.4 times higher in MCD than other glomerular variants (Log rank: p=0.000). While glomerular morphology impacted significantly on time to steroid induced CR (Figures 4 and 5), age (p=0.646, Log rank) and proteinuria severity (p=0.336, Log rank) did not. Overall median duration of CR was 7.0 months (1.0-93.0). Median time to first relapse was 11.0 months (95% CI: 1.11-20.89). Pair-wise comparison of times to first relapse among different morphologic types revealed no significant difference (Log rank: p=0.562); there were 30 relapses overall in 16 patients. Relapse rates in

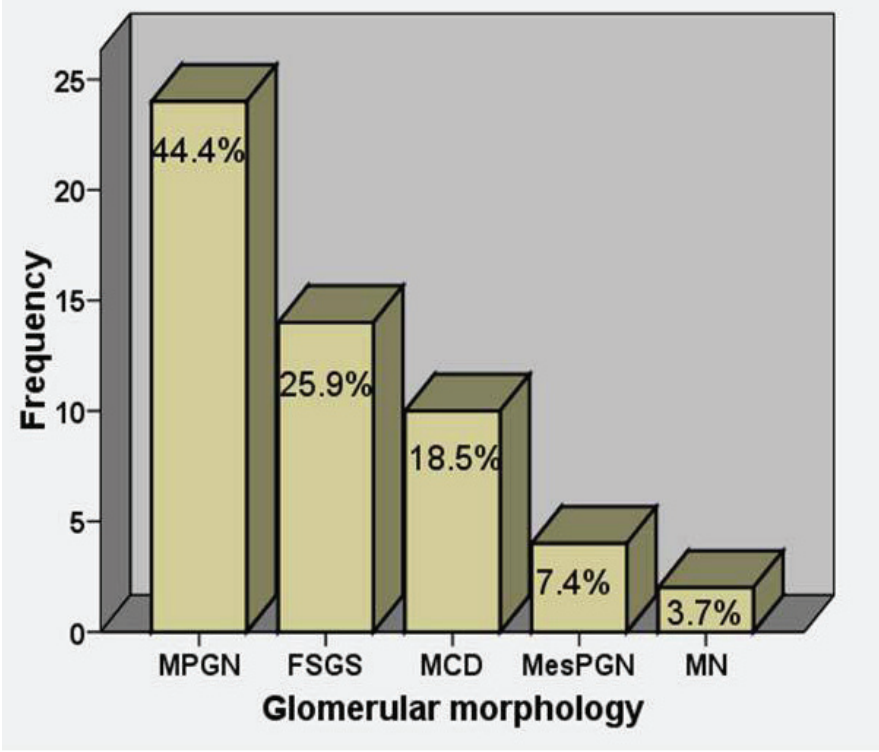

Figure 1. The prevalence of each of the glomerular morphologic variants in Nigerian children with the nephrotic syndrome; **MPGN,** membranoproliferative glomerulonephritis; **FSGS,** focal segmental glomerulosclerosis; **MCD,** minimal change disease; **MesPGN,** mesangial proliferative glomerulonephritis; **MN,** membranous nephropathy.

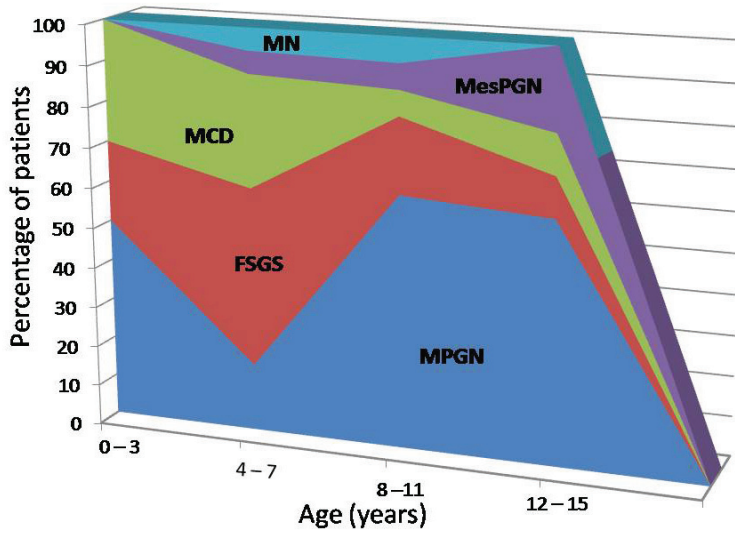

Figure 2. Percentage variation of the different glomerular morphologic subtypes with pediatric age groups; The incidence of MCD decreases with increasing age while that of non-MCD increases with increasing age. **MPGN,** membranoproliferative glomerulonephritis; **FSGS,** focal segmental glomerulosclerosis; **MCD,** minimal change disease; **MesPGN,** mesangial proliferative glomerulonephritis; **MN,** membranous nephropathy.

Table 3. Relation between the glomerular morphologic types and some clinicolaboratory characteristics (n= 54)

Clinicolaboratory Characteristics	Glomerular morphologic types[a]					% of total N = 54	P value[b]
	MCD	FSGS	MPGN	MesPGN	MN		
Baseline hypertension	2	3	11	2	0	33.3	0.080
Microhematuria	3	5	8	1	0	31.5	0.220
Reduced eGFR at baseline	3	7	12	3	0	46.3	0.220
Primary steroid resistance[c]	1	9	11	2	2	46.3	0.037

[a] **MCD,** minimal change disease; **FSGS,** focal segmental glomerulosclerosis; **MPGN,** membranoproliferative glomerulonephritis; **MesPGN,** mesangial proliferative glomerulonephritis; **MN,** membranous nephropathy.

[b] P value was derived by multinomial logistic regression analysis. Primary steroid resistance was significantly commoner with non-MCD than MCD. Other characteristics were similar in both groups.

[c] This is comprised of patients with partial remission (n= 14) and those who failed to respond to prednisolone treatment (n= 11).

MCD, MPGN, and FSGS were 77.8%, 66.7% and 33.3%, respectively. Overall cumulative relapse-free rates were 48.7%, 35.5%, 26.6%, 26.6% and 26.6% at 1, 2, 3, 4 and 5 years, respectively. The sixteenth patient relapsed at the end of 93 months. In FRNS and SDNS patients remission was maintained with cyclophosphamide (n= 3), lisinopril (n= 2; a patient converted to valsartan due to lisinopril-induced cough), valsartan (n= 2; a patient converted to spironolactone due to valsartan-induced acute kidney injury; also received HMG – CoA reductase inhibitor, fluvastatin for hypercholesterolemia, 17.0 mmol/L) and levamisole (n= 2) following CR with short courses of prednisolone. Figure 6 shows the complications of steroid therapy.

The overall median renal survival time was 42.0 months (95% CI: 30.7-50.3). Renal survival times were similar in all morphologic types (Log rank: p=0.939); overall proportions with normal renal function at 1, 2, 3, 4, and 5 years were 91.3%, 83.7%, 75.3%, 32.3% and 16.1%, respectively. Poor renal outcome was respectively found in 5 (55.6%), 2 (22.2%) and 2 (22.2%) patients with MPGN, FSGS and MCD. Of the 9 patients with poor renal survival, 5 had stage 2 CKD (eGFR: 62-78 mL/ min/1.73m^2) while the remaining 4 patients had stage 3 (eGFR: 39-59 mL/ min/1.73m^2). The rest had stages 1 to 2 CKD.

Mean eGFR at end of study was 96.3 ± 31.7 (39-153) mL/ min/1.73m^2. Median proteinuria by UPCR, plasma albumin and cholesterol were 13.2 (5.1-18.5) mg/mmoL, 40.0 (38.0-60.0) g/L and 4.5 (3.2-6.0) mmol/L, respectively. Ten of 25 (40.0%) CR patients achieved steroid-free CR. Median steroid-free CR period was 12.0 months (0.4-91.0). All CR patients were followed-up for 6-93 (median, 22.0) months.

Discussion

Expressed as percentage of pediatric admissions, the overall incidence of NS in this study is 32 – 63 times higher than that from the UK (0.04%),

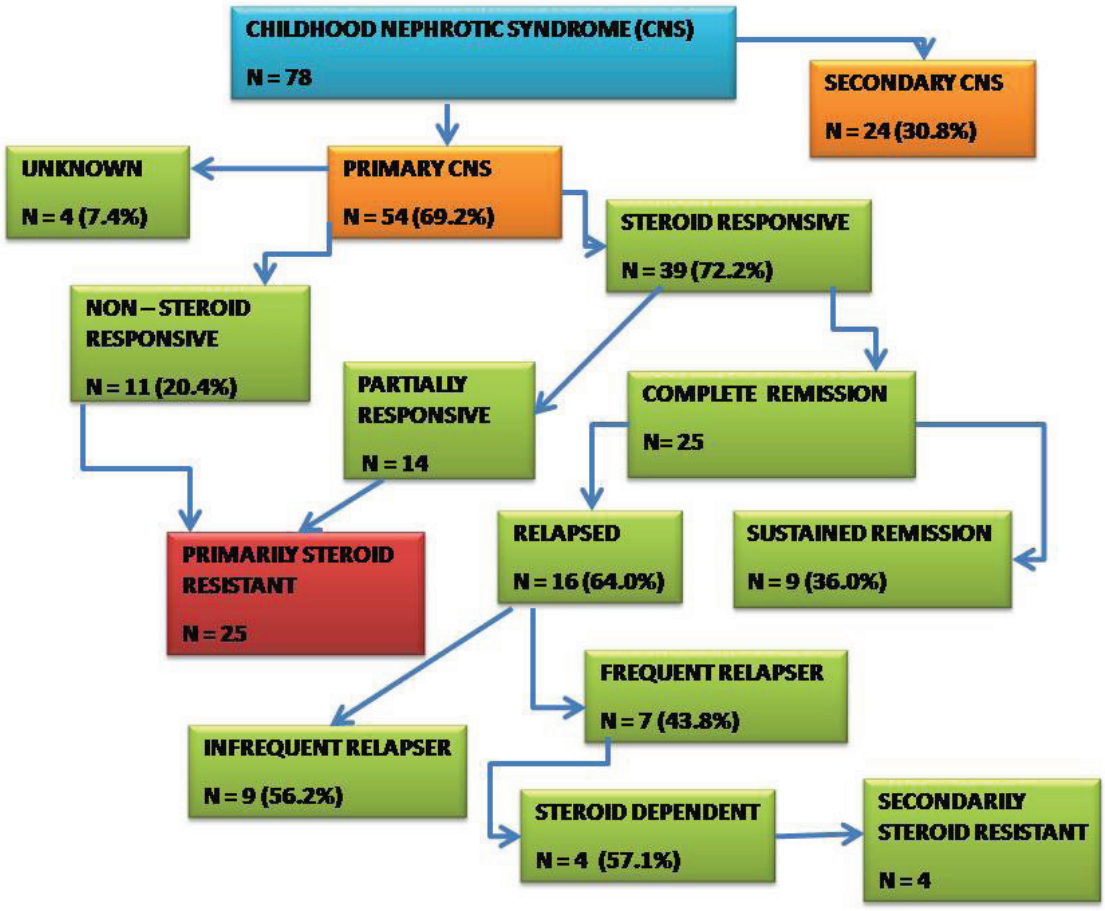

Figure 3. Flow chart showing the different levels of patients' response to prednisolone therapy.Patients who were non-responsive to prednisolone and those who were partially responsive were grouped together as primarily steroid resistant. The unknown patients were those who failed to complete at least 4 weeks of prednisolone therapy and were subsequently lost to follow-up.

US (0.03%) and China (0.02%) (1). This tandem with the pattern from developing countries where the incidence of childhood NS (CNS) is higher (1). ICNS prevalence (69.2%) in this study which parallels a recent finding in this country (71.4%) (29) demonstrates a remarkable reversal of an earlier pattern from Nigeria where secondary NS due to QMN accounted for 81.0% of all cases of CNS (11). Relatively better life-style measures, improved malarial vector control and healthcare access could have accounted for this reversal. We observed a median onset age of 7.1 years with 72.2% of the patients being 5 years old and older. This varies with onset age in Asia, Europe and North America where most cases occur under 6 years of age (5-7) due to MCD predominance. MCD was found commonly among very young children while the non-MCD variants were predominantly found among older children in this study (Figure 2). This is similar to findings elsewhere (5-7). High frequency of HTN, renal insufficiency and hematuria observed at baseline in this study reflects non-MCD predominance. These are common features of non-MCD (5-7). Only 3.6% of the patients had severe tubulointerstitial score; this probably explains why time to CR was not influenced by tubulointerstitial injury severity. Non-MCD prevalence (81.5%) in this study is similar to the 90.2% from an earlier study from this country

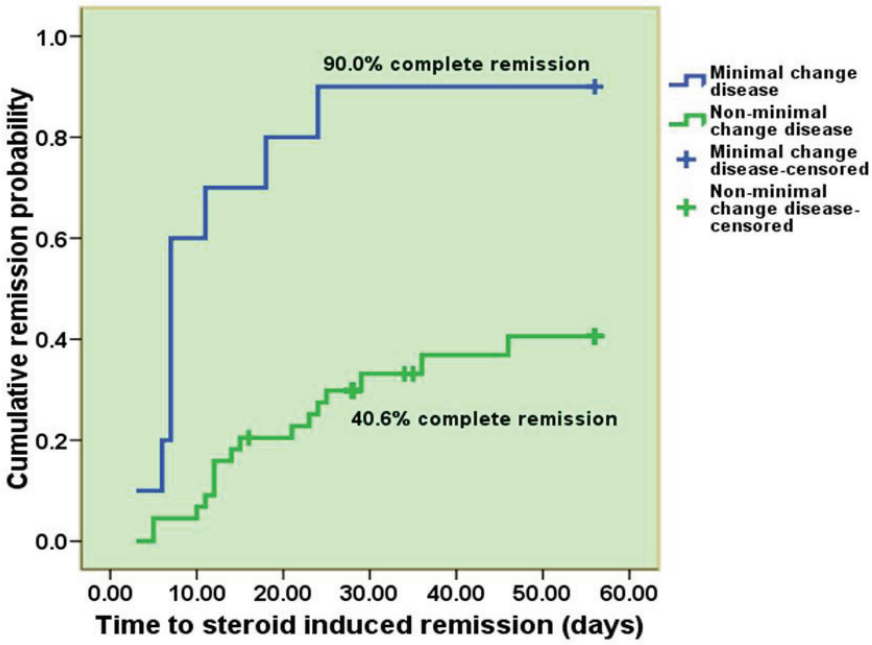

Figure 4. Survival curves comparing outcome of prednisolone treatment in patients with minimal change disease (MCD) with non-minimal change disease (non-MCD). Patients with non-MCD were significantly less steroid responsive (Log rank p=0.000); similarly, treatment survival times were significantly longer in non-MCD. Median treatment survival time for both groups was 7 days (95.0% CI: 6.24-7.76).

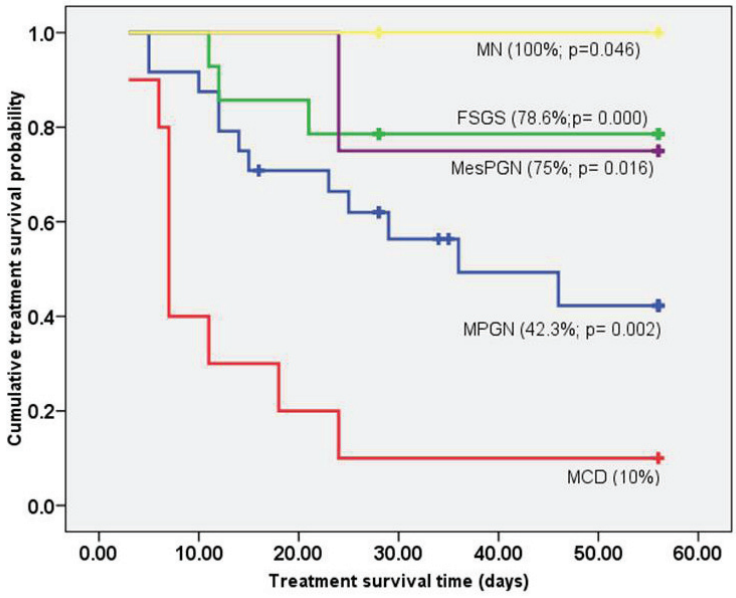

Figure 5. Kaplan-Meier survival curve showing the probabilities of treatment survival in each of the glomerular morphologic variants. The minimal change disease (MCD) is significantly less steroid resistant compared to other lesions. **MPGN,** membranoproliferative glomerulonephritis; **FSGS,** focal segmental glomerulosclerosis; **MesPGN,** mesangial proliferative glomerulonephritis; **MN,** membranous nephropathy.

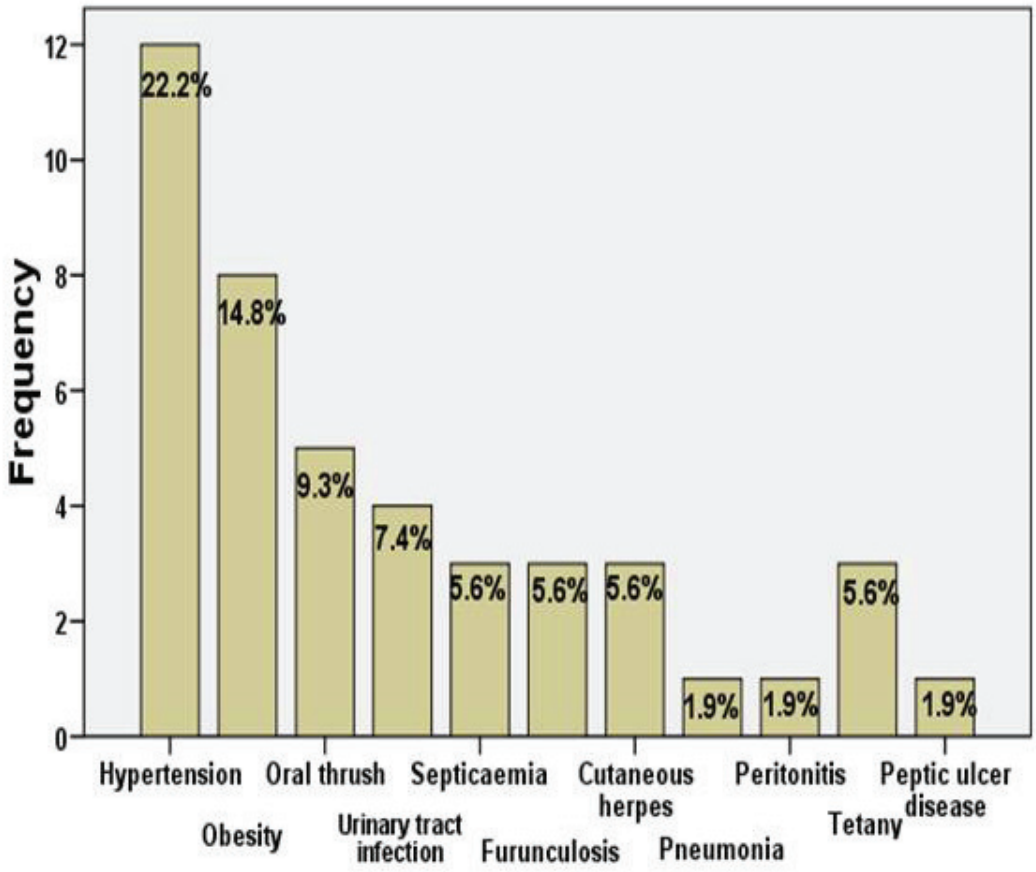

Figure 6. Complications of prednisolone treatment

(15). While MPGN (51.2%), MCD (9.8%) and MN (9.8%) were the major lesions in the latter, MPGN (44.4%), FSGS (25.9%) and MCD (18.5%) were the major histopathologic lesions in this study. Both findings reverse the well known QMN predominance pattern in southwestern Nigeria (11); furthermore, these findings contrast sharply with studies in Asians, Europeans and North Americans in which MCD accounted for 76.4-90% of all cases (5-7). Although the overall 49.6% cumulative CR rate observed in this study is lower than the 80.0-90.0% CR rate reported in other populations (reviewed by Hodson et al (2) and Bargman (3)), it is a remarkable departure from the past as childhood NS was previously associated with dismal steroid response in southwestern Nigeria with most patients reaching end-stage renal disease and dying within five years of NS onset (11). Our lower CR rate was due to non-MCD predominance while the higher CR rate in non-Africans was due to MCD predominance. While glomerular morphology impacted significantly on time to CR with MCD attaining CR fastest, age and proteinuria severity did not. The 90.0% CR rate associated with MCD in this study is therefore in keeping with well known features of this lesion (6, 7, 14). Like in other studies (76.0-97.0%) (9, 10), our relapse rate was very high, and most frequent with MCD; the 5-year relapse-free rate was 26.6.0%. Our low 5-year renal survival rate reflected MPGN and FSGS preponderance that run a relentlessly aggressive course unlike the benign MCD. Use of maintenance steroid-sparing agents may explain why none of the patients with poor renal survival reached stage 4 or 5 CKD. Infections and steroid-induced HTN that were the major complications in our patients were satisfactorily managed without mortality.

Conclusions

High prevalence of aggressive features like HTN, hematuria and renal insufficiency and the 42.3-100.0% steroid resistance exhibited by the predominant non-MCD variants (Figure 5) in this study strongly suggest the need for routine pre-treatment renal biopsy in our patients. The International Study of Kidney Disease in Children's (ISKDC) (12) report upon which the non-routine renal biopsy policy is based owing to MCD predominance and high steroid sensitivity excluded data from Africa; data emerging from Africa suggest that the ISKDC policy may not apply to black African children with NS (11, 12, 14, 15, 18-24); routine renal biopsy as is the practice in adult patients owing to non-MCD predominance (30, 31) will be more appropriate in our patients.

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Financial disclosure:

None.

Conflict of Interest:

None to declare.

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