

Nephrotic syndrome among children in Kano: A clinicopathological study

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Abstract

Objective: To evaluate the clinicopathological features of children with nephrotic syndrome seen in a pediatric nephrology unit in northern Nigeria.

Materials and Methods: All children less than 15 years of age who had nephrotic syndrome and who had been subjected to renal biopsy at Aminu Kano Teaching Hospital, Kano, were studied. Their histologic diagnoses were evaluated alongside clinical and other laboratory parameters.

Results: Twenty children, 17 males and three females, were studied. These represented 55% of all children with nephrotic syndrome seen in the pediatric nephrology unit during the study period, the rest of which have never had renal biopsies. Peak age was 7-8 years (range 2.5-13 years). Fourteen of the 20 children (70%) had previously been on steroid treatment. Of these, 11 (55%) were classified to be steroid resistant and three (15%) were frequent relapsers. Six (30%) children were newly diagnosed with nephrotic syndrome and had not commenced steroid treatment. Hypertension was found in seven (35%) children. Sixteen children (80%) had microscopic hematuria on presentation. The most common histopathological diagnosis was focal glomerulosclerosis in nine (45%) children (segmental = 8; global = 1). Minimal change disease was found in four children (20%), membranoproliferative glomerulonephritis in three children (15%), membranous nephropathy in three children (15%), and diffuse mesangial hypercellularity in one child (5%). Of the six children who had renal biopsy before commencement of steroid treatment, three (50%) were found to have glomerulosclerosis.

Conclusion: Focal segmental glomerulosclerosis was the most common histological subtype diagnosed in Kano among children with nephrotic syndrome in this study.

Key words: Focal segmental glomerulosclerosis, Kano, nephrotic syndrome, pediatrics

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Introduction

Nephrotic syndrome is a clinical condition characterized by massive proteinuria, hypoalbuminemia, hypercholesterolemia, and generalized edema.^[1] It occurs more commonly in children than in adults, and usually manifests as one of two usually idiopathic diseases: Minimal change nephrotic syndrome (MCNS) or focal segmental glomerulosclerosis (FSGS).^[2] Other histological patterns of nephrotic syndrome seen in children include membranoproliferative glomerulonephritis (MPGN),^[3-5] and rarely membranous nephropathy (MN)^[2] and diffuse mesangial hypercellularity (DMH).^[5,6] MCNS has been

documented to be the most common histopathological lesion in children, especially in temperate regions, and it generally has a favorable response to glucocorticoid therapy in over 80% of patients.^[6-9] Children having steroid-resistant nephrotic syndrome (SRNS) with focal and segmental glomerular sclerosis (FSGS) or MCNS run a high risk of resistance to immunosuppressive therapy.^[10] The incidence of FSGS appears to be on the increase with environmental pollution and morbid obesity being proposed as hypothetical reasons.^[11-17]

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Ethnic origin may affect the histological variant and the response to immunosuppressive treatment. In particular, Hispanic and black patients have been shown to be more likely to have steroid-unresponsive nephrotic syndrome than are white patients.^[18] Studies from Pakistan,^[4] Iran,^[5] Turkey,^[8] Canada,^[14] Nigeria,^[19-21] Ghana,^[22] South Africa,^[23] and the USA^[18,24] have also documented varying experiences, with reports favoring the non-MCNS types. These non-MCNS types are known to have atypical clinical presentations and are less responsive to steroids when compared to MCNS.^[6,18,23]

There is a paucity of literature on the pattern of nephrotic syndrome in northern Nigeria. This review aims to evaluate the clinicopathological findings in children who had renal biopsy in Kano, northwestern Nigeria, with a view to documenting the prevalent histopathological types in this environment.

Materials and Methods

Aminu Kano Teaching Hospital (AKTH), established in 1988, is a tertiary center in Kano, northern Nigeria whose clientele includes patients from Kano state and several surrounding states including Zamfara, Katsina, Jigawa, Bauchi, Gombe, and Yobe states. The renal biopsies are carried out by the pediatric nephrologist and all slides are reviewed by the pathologists using light microscopy with several stains. The center has no facilities for immunofluorescence or electron microscopy.

Clinical and laboratory data as well as histology results were retrieved from case notes of children with clinical features of nephrotic syndrome who had renal biopsy. Information obtained included age at diagnosis; gender; blood pressure; urinalysis findings; serum proteins; serum chemistry; serology results for hepatitis B, C, and human immunodeficiency virus (HIV); and renal biopsy results. Hypertension was defined as elevated systolic and/or diastolic blood pressure above the 95th percentile for age, gender, and height.^[25]

Following unit protocols, the children who had renal biopsy were those who had remained unresponsive to initial steroid therapy of more than 6 weeks, who had more than three relapses in a 1 year period, who had atypical features of nephrotic syndrome at the time of diagnosis before the commencement of steroid treatment, and those whose caregivers consented to renal biopsy, as well as those who gave assent. All renal biopsies were performed under ultrasound guidance using spring-loaded semiautomatic biopsy needles after light sedation and application of local anesthetics. Each biopsy specimen was fixed and transported in 10% buffered formalin solution for analysis in the pathology laboratory of the hospital where they were

embedded with paraffin wax and stained with hematoxylin and eosin, periodic acid-Schiff, trichrome stain, and reticulin silver stains. Only light microscopy was performed on the tissue samples. All histological findings were reported by pathologists. Ensuing data was managed with Statistical Package for Social Sciences (SPSS) software version 16.0 for Windows.

Results

There were a total of 36 children with nephrotic syndrome being followed-up in the pediatric nephrology unit. Twenty children (55%) had renal biopsy and were included in this study. They included 17 males and three females (M:F = 5.7:1). Mean age was 8.3 ± 3.0 years. Of the remaining 16 children (eight males and eight females) who did not have renal biopsy, four (25%) had been unresponsive to steroid therapy and two were frequent relapsers. Ten children (28% of total) attained remission from initial steroid therapy, and had remained in remission.

The clinical and laboratory characteristics of the patients before biopsy as shown in Table 1 demonstrate that 16 children (80%) had microscopic hematuria. Seven children (35%) had hypertension. Six children (30%) tested positive to hepatitis B surface antigen (HBsAg), while antibody to hepatitis C virus (anti-HCV) was also positive in three of them. One child (5%) was seropositive to HIV.

The indications for renal biopsy were SRNS in 11 (55%) children, presence of atypical features pre-steroid treatment in six (30%) children, and frequently-relapsing nephrotic syndrome in three (15%) children. The atypical features seen in the 6 children included hypertension, microscopic hematuria, and renal failure.

The summary of the histopathological diagnoses for the study population is shown in Table 2.

There was no statistically significant association between gender or age ≤ 8 years and the histopathological type of NS (gender: $\chi^2 = 7.908$, $P = 0.161$; age ≤ 8 years: $\chi^2 = 4.722$, $P = 0.451$). The most common histological diagnosis was FSGS in eight (40%) children.

Of the 11 children with SRNS, six (54.5%) had FSGS, three (27.3%) had histopathological features suggestive of MCNS while one each (9.1%) had MN and MPGN.

The six children who had renal biopsy before commencement of steroid therapy all (100%) had hematuria on initial presentation. Four of them (66.7%) had hypertension and two (33.3%) had clinical and laboratory features of renal failure. On light microscopy of their biopsy specimens, two children each (33%) were found to have FSGS and

Table 1: Clinical, laboratory, and histopathological characteristics of the study population

Case	Age (year)	Gender	HTN	mHem	Urea (mmol/L)	Cr (μ mol/L)	Biopsy indication	Hep B	Hep C	HIV	Histology result
1	2.5	M	POS	POS	12.9	82	SR	NEG	NEG	NEG	MCNS
2	3	M	NEG	NEG	12.4	48	SR	NEG	NEG	NEG	MCNS
3	5	M	NEG	POS	5.0	45	PS	NEG	NEG	NEG	DMH
4	5	M	NEG	POS	1.4	30	SR	NEG	NEG	NEG	FSGS
5	7	F	NEG	POS	4.4	55	SR	POS	POS	NEG	FSGS
6	7	M	NEG	POS	6.2	60	PS	POS	NEG	NEG	MPGN
7	7	F	NEG	POS	8.9	31	FR	POS	POS	NEG	MN
8	7	M	NEG	NEG	3.2	32	SR	POS	NEG	NEG	MN
9	8	M	POS	POS	9.3	58	SR	NEG	NEG	NEG	MPGN
10	8	M	POS	POS	5.1	30	SR	POS	NEG	NEG	FSGS
11	8	M	NEG	POS	4.1	84	SR	NEG	NEG	NEG	FSGS
12	8	M	POS	POS	13.6	399	PS	NEG	NEG	NEG	MPGN
13	10	M	POS	POS	7.9	104	PS	NEG	NEG	NEG	FSGS
14	10	M	NEG	NEG	7.2	54	SR	NEG	NEG	NEG	FSGS
15	11	M	NEG	POS	1.9	109	SR	POS	POS	NEG	FSGS
16	11	F	NEG	POS	6.9	75	FR	NEG	NEG	NEG	MN
17	11	M	POS	POS	1.8	119	PS	NEG	NEG	NEG	FSGS
18	12	M	NEG	NEG	1.7	85	FR	NEG	NEG	NEG	MCNS
19	13	M	NEG	POS	7.1	30	SR	NEG	NEG	NEG	MCNS
20	13	M	POS	POS	16.7	884	PS	NEG	NEG	POS	DGGS

M=Male, F=Female, HTN=Hypertension, POS=Positive, NEG=Negative, μ Hem=Microscopic hematuria, Cr=Creatinine, SR=Steroid-resistant, PS=Pre-steroid, FR=Frequent relapser, MCNS=Minimal change nephrotic syndrome, DMH=Diffuse mesangial hypercellularity, FSGS=Focal segmental glomerulosclerosis, MPGN=Membranoproliferative glomerulonephritis, MN=Membranous nephropathy, DGGS=Diffuse global glomerulosclerosis, Hep=Hepatitis, HIV=Human immunodeficiency virus

Table 2: Summary of histopathological diagnoses of the study population

Histopathological type	Number (frequency) (%)
Focal segmental glomerulosclerosis	8 (40)
Suspected minimal change nephrotic syndrome	4 (20)
Membranoproliferative glomerulonephritis	3 (15)
Membranous nephropathy	3 (15)
Diffuse global glomerulosclerosis	1 (5)
Diffuse mesangial hypercellularity	1 (5)

membranoproliferative glomerulonephritis (MPGN), while one each had DMH and diffuse global glomerulosclerosis (DGGS). DGGS with histological features of end stage renal disease was seen in a 13-year old boy recently diagnosed with HIV.

The histopathologic diagnoses in the three children who had frequently-relapsing nephrotic syndrome were MN in two, and histopathological features suggestive of MCNS in one child.

All of the six children who tested positive to HBsAg had non-minimal change type of disease. FSGS was seen in three of them (50%), MN in two (33.3%), and MPGN in one child (16.7%).

Of the seven children who were found to have hypertension in this study, biopsy results revealed FSGS in three children,

MPGN in two children, and DGGS and MCNS in one child each.

Discussion

Reports on sociodemographic, geographical, and histopathological patterns of nephrotic syndrome from different parts of the world have shown variable patterns.^[2-5,14,18-23,26,27] The male preponderance in our center is similar to reports from most other studies^[4,5,19,20,22,26,28] conducted locally and worldwide, but different from findings in Port Harcourt (Nigeria)^[21] and a recent study from the USA,^[24] in which there was equal gender distribution, the proffered reason in the American study being that the initial gender disparity was eliminated when the follow-up period was extended to 25 years.^[24] The peak age of 7-8 years found in this study compares well with those of a few other studies from other parts of northern Nigeria,^[3,20,29] India^[6] and Germany.^[10] However, studies from the southern part of Nigeria,^[21,26] Iran^[5] as well as an older study from India^[28] found lower peak ages of less than 5 years, while peak ages of about 12 years were reported in studies from Pakistan,^[4] Ghana,^[22] and USA.^[24] All the children in this study were of the same racial background, therefore, no racial comparison could be made.

Hypertension as a presenting feature in 35% of all children in this study (and in 66.7 and 37.5% of those with a histopathological diagnosis of MPGN and FSGS, respectively)

was comparable to the documented findings in previous reports from Nigeria,^[21,26] Ghana,^[22] and the USA.^[24] Although higher than the 15.9% documented in a report from India,^[28] hypertension was present in almost two-thirds of the children with significant lesions in the Indian study, compared to only 2% in children with minimal lesions. In the same study, it was present in all the children with MPGN.^[28] 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.

The search for a possible etiological factor in cases of nephrotic syndrome cannot be overstressed. In the light of this, hepatitis B virus, among other viruses, has been documented as a cause of nephrotic syndrome in childhood.^[2,7,23] Seropositivity for HBsAg was high in this study; at 30%, it is comparable to the 25.3% prevalence among children attending all clinics in a previous study from this center.^[30] It is also comparable to the 24% reported in a much earlier study from northern Nigeria.^[3] However, it was much higher than the 6.5% documented in Pakistan,^[4] and zero percent documented by Safaei and Maleknejad^[5] in Iran and Anochie *et al.*,^[21] in Port Harcourt (Nigeria), although a more recent study from the same center in Port Harcourt has documented a seroprevalence rate of 12.4% among all children attending clinics in the center.^[31] The high rate of HBsAg positivity could be a reflection of the general prevalence rates in Nigeria.^[32]

The histopathological patterns of nephrotic syndrome documented by several authors have also been at variance with one another. While some studies^[11-17] have reported an increasing prevalence of FSGS, including studies from Ghana^[22,27] which have shown a similar trend over a 25-year period, Boyer *et al.*,^[18] on the other hand, in a longitudinal assessment over a 25-year period, documented a stable prevalence of FSGS, albeit with increasing age at diagnosis as well as a marked increase in steroid resistance over time. Earlier studies from some parts of Nigeria reported higher incidences of MPGN, with much lower figures for minimal change disease.^[3,19,20] However, none of these studies had FSGS as part of their histological diagnoses.

The 40% prevalence of FSGS documented in this study could be compared with that of 50% documented in biopsied patients in Port Harcourt.^[21] However, the patients who had biopsy in the Port Harcourt study were very few and may thus not make for accurate comparison. In recent studies from India and Pakistan, the most common histological diagnosis in children was FSGS.^[4,6] The picture was different in India over 3 decades ago when minimal change disease was documented to be the most commonly identified lesion.^[28] However, almost two-thirds of the patients in that study were less than 5 years of age, during which period minimal change disease is known to be most common. Furthermore, MPGN and FSGS accounted for

18 and 20%, respectively of cases with significant lesions on biopsy in that study.

MN is known to be rare in children,^[2] and was found in only three children (15%) in this study. Two of the three children (66.7%) were found to be positive for HBsAg, a feature that highlights similarity between our findings and those from South Africa^[23] particularly among the blacks in which it accounted for as much as 40% of their lesions.

Although several of the diagnostic entities rendered by light microscopy and histochemistry are often generally straight forward, this study was limited by the inability to carry out immunofluorescence and/or electron microscopy on the kidney tissue specimens. These would have been of tremendous value in subclassifying and detailing the immunopathological and cellular features of the diagnosed entities. Since three of four children with light microscopy features suggestive of MCNS in this study were steroid-resistant from the outset, it is possible that they were milder forms of FSGS or other histological types, and may have been possibly better evaluated if further tests could have been carried out on the biopsy specimens.

Conclusion

In conclusion, even though there appears to be no single histological entity that underlies nephrotic syndrome among blacks in Nigeria and Africa in general, the incidence of non-minimal change patterns of nephrotic syndrome, particularly FSGS, appears to be increasingly assuming greater importance. In this study, FSGS was found to be the most common histopathologic type among children diagnosed with steroid-unresponsive nephrotic syndrome who had renal biopsy in AKTH, Kano. It was also common in children presenting with atypical features of nephrotic syndrome. This portends a poorer prognosis as FSGS is more commonly steroid-resistant, with a propensity to lead to end stage renal disease. There is a need for a prospective study with a larger sample size to further corroborate the findings in this study.

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