**CLINICO-PATHOLOGIC STUDY OF CHILDREN/YOUNG ADULTS WITH NEPHROTIC SYNDROME IN PORT HARCOURT, NIGERIA.**

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*Abstract.*

Background: As renal diseases continue to contribute significantly to the burden of morbidity and mortality in Nigeria, data on clinico-pathologic features of kidney diseases, especially among children remains scanty. This retrospective study evaluated the clinico-pathological findings in children with nephrotic syndrome in Port Harcourt, Nigeria between 2014 and 2015.

Materials and methods: The demographic/clinical information of the patients and light microscopy of the formalin fixed tissues, sectioned at 3 levels and stained with H& E and special stains were evaluated.

Results: Nineteen patients, comprising 10 (52.6%) females and 9 males (47.4%) underwent percutaneous renal biopsy (PRB) within the period of review. The age range and mean were 1.8 to 21 and 11.0 +- 6.5 years respectively. There was a steady decrease in number of biopsied patients with age below 15 years but above 15 years presented the highest number of cases (36.1%). Eleven of the patients (57.9%) were steroid dependent (SDNS) while 8 cases (42.1%) were steroid resistant (SRNS). Hypertension and hematuria occurred more in SDNS (63.6% vs 45.5%) as against (25% vs 25%) respectively in SRNS. Non-proliferative lesions (NPL) which included minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and collapsing glomerulopathy (CG) predominated with 11 cases (57.9%) over proliferative lesions (PL), composed of membranoproliferative glomerulonephritis (MPGN), mesangioproliferative glomerulonephritis (MSPGN) and MPGN with collapsing glomerulopathy (MPGN +CG) with 8 cases (42.1%). Among NPL, MCD and FSGS occurred in equal proportions of 4 cases (36.4%) each while CG occurred in 27.2%. The PL were composed majorly of MPGN (62.5%) followed by MSPGN (25%) and MPGN +CG (12.5%). The single most common pathologic diagnosis was MPGN with 5/19 26.3%. While 62.5% of patients with proliferative lesions presented with hypertension, only 36.4% of patients with non-proliferative lesions presented with hypertension.

Conclusion: Renal biopsy practice is inadequate in Port Harcourt. Although MPGN is the most common cause of NS in Port Harcourt children, collapsing glomerulopathy in HIV negative children also contributes significantly. There is need for increased utility of PRB in nephrology practice in order to optimize patient management in Port Harcourt.

Key words: Kidney, Biopsy, Children, Port Harcourt

***Introduction.***

Renal diseases which affect children are heterogeneous and the pattern varies from one geographic region to another.1,2 Genetic predisposition, environmental background and the level of awareness about the diseases are some factors that influence this variability 3.

That nephrology practice is still evolving in Nigeria especially among paediatricians, is attested to by the relative paucity of percutaneous renal biopsies (PRB) even among deserving patients. This is in spite of the fact that PRB is generally considered a safe procedure in pediatric patients 1. This is attributed by some authors to the assumption by clinicians that nephrotic syndrome in children is majorly due to Minimal Change Disease (MCD) and hence, steroid therapy is instituted empirically on clinical grounds 4,5.

Moreover, renal biopsy in pediatric group is more demanding than the adult counterpart owing to the expertise required for handling apprehensive children and concerned parents 6. Consistent with this notion is a publication from Jordan that indicated that pediatric kidney biopsy does not exceed 10% of the total biopsies 1. In addition, patients in our environment often find it difficult to pay for the necessary fees required for the execution of a renal biopsy procedure including admission, procedure and histology fees.

However, histological examination of renal biopsy is not only fundamental in establishing the clinical diagnosis, but also provides insight into the histological pattern and prognosis of renal disease and guides treatment 6. Common indications for renal biopsy include: Unexplained renal failure, Acute nephritic syndrome, Nephrotic syndrome, proteinuria, hematuria, Renal masses (primary or secondary), monitoring of allograft kidneys, Connective-tissue diseases (eg, systemic lupus erythematosus) 7.

Typically, renal biopsy is analysed for preliminary pathological diagnosis by systematically examining the different histologic compartments (glomeruli, tubules, interstitium, and blood vessels) under light microscopy using tissue sections routinely stained with H&E and special stains, after a review of the clinical information of the patient. However, when the light microscopic findings are complemented with immunofluorescence/immunohistochemistry and electron microscopy, a more accurate and conclusive diagnosis is made. The latter services are not available in most centres of Nigeria, including ours.

This constitutes an impediment to accurate pathological diagnosis of renal biopsies in our environment. 8, 9. Nonetheless, well processed and stained tissue sections evaluated by experienced nephropathologist using light microscopy yields dependable pathologic diagnosis which remains an important guide for the clinician in the diagnosis, prognosis, and therapy of renal disease in deprived environment such as ours.

As renal diseases continue to contribute significantly to the burden of morbidity and mortality in Nigeria, data on pathology of kidney diseases remains very scanty due to paucity of renal biopsy tissue in histopathology labs and dearth of nephropathologists in Nigeria 10, 11.

This study, therefore, evaluated the spectrum of pathological findings in children who presented with symptoms requiring renal biopsies in our centre in Port Harcourt, Nigeria.

***Materials and methods.***

This is a retrospective review of all percutaneous renal biopsies processed at the University of Port Harcourt Teaching Hospitals Port Harcourt, (UPTH) Nigeria, between January 2014 and December 2015. UPTH is the foremost tertiary health institution in the Niger Delta region/South-South part of Nigeria and enjoys patients’ patronage from the neighbouring states of Abia, Imo, AkwaIbom, Bayelsa, Delta, Edo and Cross River. The caregivers/parents of all patients consented to renal biopsy of their wards/children. All renal biopsies were performed under ultrasound guidance using spring‑loaded semiautomatic biopsy needles after light sedation and application of local anaesthetics. The patients were treated as day cases and returned home after 5-8 hours of uneventful post biopsy monitoring.

The demographic and relevant clinical details of the patients were gleaned from their pathology request cards and case notes, where available. The information sought for included: age at diagnosis, gender, blood pressure, urinalysis findings, serum chemistry results, serology results for hepatitis B, C, and human immunodeficiency virus (HIV). The biopsies were fixed in 10% neutral buffered formalin processed using automated tissue processor, embedded in paraffin wax and sectioned at thickness of 2–4 µ and stained with hematoxylin and eosin (H and E), periodic acid Schiff (PAS), Jones methenamine silver (JMS) and Masson's trichrome (MS). Three levels of the tissue sections were made for each of the stains. Where indicated, Congo red stain was applied on the tissue sections. Appropriate positive controls were used to validate each of the special stains. The biopsy sections were all histologically reviewed and reported by one nephropathologist for preliminary pathological diagnosis by systematically examining the different compartments (glomeruli, tubules, interstitium, and blood vessels) at three levels of tissue sections. The histologic diagnoses were grouped as glomerular and non-glomerular lesions, depending on the compartment majorly involved by histopathologic lesions. The glomerular lesions were classified using the World Health Organization classification scheme 12. The non-glomerular lesions involved tubulointerstitial nephritis and acute tubular injury (ATI) as well as vascular lesions.

The results were analyzed for differences in proportion using Chi-square by the Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). The frequencies of cases were expressed as percentages. The level of statistical significance was set at P ≤ 0.05.

This study was approved by the ethical committee of our institution.

***Results***

Ten and 8 patients underwent PRB during the 2014 and 2015 workshops respectively while another case was subsequently biopsied in 2015, bringing the total number of cases analysed in this study to 19. Of these, 10 cases (52.6%) were females Table 1. The age range was 1.8 to 21 years. The mean and median ages were 11.0 +- 6.5 and 11.0. Age distribution of patients showed a steady decrease in number of biopsied patients with age from 0-5 years age bracket, through 6-10 years and 11-15 years. However patients who were older than 15 years presented the highest number of cases, amounting to 36.1%. The peak age was 17 years. Figure 1.

The indication for all biopsies was nephrotic syndrome and 11 cases (57.9%) were steroid dependent while 8 cases (42.1%) were steroid resistant. Figure 2. Majority - 63.6% of the steroid dependent nephrotic syndrome were females while majority of the steroid resistant nephrotic syndrome – 62.5% were males. Table 2. While the incidence of steroid dependent nephrotic syndrome varied with age, that of steroid resistant did not. Figure 3 Hypertension occured more with SDNS (63.6%) unlike SRNS (25%). This is contrary to the findings of proteinuria where both conditions exhibited significant proteinuria; although SRNS showed higher percentatage of occurrence – 75% vs 63.6%. Table 4 Hematuria occurred more among SDNS than SRNS (45.5% vs 25%). Table 5 In both conditions, oliguria was an uncommon feature – having presented in only 36.4% and 37.5% in SDNS and SRNS respectively. Table 6 Majority of the cases that presented with oliguria 57.1% showed histologic features of collapsing glomerulopathy.

The glomerular lesions were grouped into proliferative lesions, composed of membranoproliferative glomerulonephritis (MPGN), mesangioproliferative glomerulonephritis (MSPGN) and MPGN with collapsing glomerulopathy (MPGN +CG) and the non-proliferative lesions which in turn included minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and collapsing glomerulopathy (CG). There were more of non-proliferative lesions – 11 cases (57.9%) than proliferative lesions (42.1%). Table 7 The former were composed of MCD and FSGS occurring in equal proportions of 4 cases (36.4%) each as well as CG which constituted 27.2%.

The latter were composed majorly of MPGN (62.5%) followed by MSP (25%) and MPGN +CG (12.5%). Table 7 The single most common clinical diagnosis was MP with 5/19 26.3%. For proliferative lesions, gender ratio was skewed in favour of females with MFR of 1:3.5 while that of non-proliferative lesions was skewed in favour of males with MFR of 1:0.5. While 62.5% of patients with proliferative lesions presented with hypertension, only 36.4% of patients with non-proliferative lesions presented with hypertension.

The mean duration of sickness prior to presentation to the clinic was 22.2 months, minimum period was 1 month while maximal duration was 132 months.

All the biopsies were adequate and contained renal cortex and medulla. There was no case of post-biopsy complication. On the average, 17.5 glomeruli were examined in each biopsy, with range of 0-39.

***Discussion.***

Percutaneous renal biopsy (PRB) is generally considered a safe procedure in pediatric patients 1. Inspite of this, the two years under review showed only 19 patients who underwent renal biopsy in our centre. This indicates poor practice of renal biopsy in our centre which is the foremost tertiary health facility in the south south region of Nigeria, with a catchment of vast population of over 10 million people covering 3 states, of which a significant burden of renal diseases exists. To buttress this point, an earlier study carried out in our centre by Anochie et al indicated that of 28 children with nephrotic syndrome, only 4 (14.2%) underwent renal biopsy and therefore had pathological diagnoses. 13 Similarly, Asinobi et al in a study in Ibadan South West of Nigeria over an eight year period (2006-2013) yielded only 56 PRB in children. Although they noted that, not all patients who merited biopsy had the procedure carried out on them as a result of inadequate funding. 14

Moreover, Okpechi et al in their epidemiological review and meta-analysis study of renal biopsies observed poor rate of renal biopsies across Africa and attributed this to out of pocket payments for medical services by patients and dearth of skills for renal biopsy performance, handling of tissue and adequate interpretation of histology. 15 However, other studies in other centres in Nigeria have shown significant numbers of renal biopsies, like in Ile Ife South West of Nigeria, a retrospective review showed incidence of 264 biopsies in 10 years while in Kano North West of Nigeria, a similar review revealed 36 renal biopsies in a year. 16, 17 Selectivity of renal biopsy performance in pediatric nephrology patients is a global practice that is not restricted to our environment and so will not explain the paucity of biopsies in our centre.

Considering that histological examination of renal biopsy samples is not only fundamental in establishing clinical diagnosis, but provides insight into the histological pattern and prognosis of renal disease and guides treatment, efforts should be intensified by the relevant government agencies and international development partners and donor agencies at ensuring an improvement in the care of nephrology patients especially among the paediatric age group. This can be done through the provision and training of expert manpower in nephrology as well as the essential diagnostic infrastructure like immunofluorescence and electron microscopy.

The mean age of 11.0 years observed in this study while comparing favourably with 11-12 years reported in Ghana, Pakistan and USA 18-20, is well above 7-8 years previously reported in various centres within Nigeria including Zaria, Kano and Enugu 17,21,22 as well as in South Africa 23 . Other studies even reported lower mean age of 5 years within and outside Nigeria 13,24-26. This marked variation in mean age across different geographic and ethnic divides possibly relates to the differences in the inclusion criteria of the patients or reflect the influence of environment in the pathology of renal disease. The reason behind the steady decrease in number of patients biopsied with increasing age with a sharp increase of cases from 15 years age group with peak of 17 years is unclear to us. However the relatively small sample size of our study may have affected the statistical outcome.

Gender disparity in kidney biopsy studies is inconsistent and varies across and within geographic and ethnic divides. However, while most reports indicate male predominance, 16,17,27, 28 few reported female preponderance 29 and yet another show equal sex predilection. 13 Our marginal predominance of females over males on the overall is therefore agreeable with a few previous studies carried out outside Nigeria but not consistent with the majority of study findings within and outside Nigeria. This may imply that the erstwhile notion that parenchymal renal damage and the resultant chronic renal disease is more common in males is not obtainable in our centre. This is more so as the previous researchers from our centre have found equal male and female involvement in paediatric nephrology patients. 13 The predominance of females among patients with proliferative glomerular lesions is also striking and is in keeping with the findings by Onwubuya et al in Ile Ife who reported that of all the glomerular lesions encountered in the study, only MSPGN showed a higher number of cases in females. 17 The predominance of proliferative lesions in females was attributed to the relatively high proportion of lupus nephritis in those studies 16,27,30. This was not true in our study as none of the cases had lupus.

Globally, there is poor consensus on the indications of PRB with the attending consequence that renal biopsy performance is based on personal opinion and/or single-center policies. 31 For instance, in Ibadan, there has been a shift in the indication in paediatric patients based on time trend of prevailing causes of nephrotic syndrome. 14 In most similar studies in Nigeria including our centre, nephrotic syndrome remained the most frequent indication for PRB. In this study, steroid dependent nephrotic syndrome (SDNS) constituted 57.9% and steroid resistant constituted 42.1%. The earlier clinical studies carried out in my centre indicated high level of steroid response. 13,24. Since the steroid responsive patients could become steroid dependent over time, our finding of more cases of steroid dependent than responsive is consistent with the earlier studies carried out in our centre. On the contrary, studies conducted in Ibadan and Kano, Nigeria as well as India showed preponderance of SRNS over SDNS 14,17, 26. In some western countries including France, Finland and Italy, the commonest indication for PRB is asymptomatic urinary abnormalities (AUA) 31.

The higher occurrence of hypertension and hematuria in SDNS contrasts with the work done in Kano, Nigeria which showed that 80% of SRNS patients had hematuria. 17 This difference is probably related to environmental influence on the different study populations. Overall, oliguria is not common and the majority of the cases recorded were seen among the collapsing glomerulopathy.

That all the biopsies were on native kidneys, devoid of allograft biopsy is consistent with most other studies earlier carried out in Nigeria. This suggests that kidney replacement therapy is still alien in Nigeria especially among the paediatric age group.

Of the four normal histologic compartments of the kidney, glomerular lesions were the underlying pathology in all the cases in our study. This is consistent with reports from previous researchers and underscores the importance of glomerular lesions in the pathogenesis of kidney disease especially in children. 16,32,33

Grouping the microscopic diagnoses of the glomerular lesions into proliferative lesions, was based on the presence of inflammatory activity which together with the associated increase in the number of endothelial cells, or mesangial cells present the picture of hypercellular glomerular tuft on LM. They are composed of membranoproliferative glomerulonephritis (MPGN), mesangioproliferative glomerulonephritis (MSPGN) and MPGN with collapsing glomerulopathy (MPGN +CG) while the non-proliferative lesions included minimal change disease (MCD), Focal segmental glomerulosclerosis (FSGS) and collapsing glomerulopathy (CG).

In their review study of proliferative glomerulonephritis in New York, Samih et al observed that monoclonal immunoglobulin deposition including – heavy and light chain deposition diseases, type 1 cryoglobulinemic glomerulonephritis, immunotactoid glomerulonephritis, and light and heavy chain amyloidosis constituted the underlying pathology in their series. 34 On LM review, Samih et al noted that 56.8% of the proliferative glomerulonephritis displayed MPGN features consisting of double-contoured glomerular capillary walls and hypercellularity, which is similar to the LM findings of proliferative glomerulonephritis in our study. Although their patients were adults, it is arguable that these dysproteinemia based pathologies could also occur among children. Unfortunately, owing to limitation in diagnostic infrastructure, we are unable to rule out those disease entities in our environment. Proliferative glomerulonephritis is a sequele of direct and indirect infectious processes involving the kidney like post-infectious glomerulonephritis, especially in our environment where as a result of the generally poor environmental conditions and the pervading poverty, children are frequently exposed to infectious conditions. 35,36 Thus the finding of more non-proliferative lesions in this study tells of the significance of non-proliferative lesions including FSGS, MCD and CG in the pathogenesis of kidney diseases in our environment at this time.

However, this is at variance with report of a study in Saudi Arabia. 36 Specifically, FSGS and MCD constituted the highest diagnostic lesions – constituting 36.4% each. While the high incidence of FSGS is consistent with previous reports from our centre and other centres in Nigeria, 13,14,17 the associated high incidence of MCD is inconsistent with most previous works in Nigeria which reported low incidence of MCD 28,37,38 This change in trend is comparable to the observation in Ibadan by Asinobi et al who noted a progressively increasing incidence in FSGS over decades, overtaking quarter malaria nephropathy (QMN) and MPGN to become the most prevalent pathological lesion responsible for childhood NS in Ibadan as at the time of their study 14. They attributed this to a possible change in the aetiological factor of NS. Similarly, we have observed an increase in incidence of MCD from the previous report from our centre that recorded low incidence of MCD. 13 Like averred by Asinobi et al, this is likely an indication of a change in the aetiopathogenesis of NS in our environment. However, further studies are needed to validate this finding and probe into the aetiopathogenesis considering also, the relatively low number of reviewed biopsies in this study.

That CG constituted 27.2% of the diagnoses is significant in view of the perceived association of CG with HIVAN. Unfortunately, none of the patients were HIV positive. Although Albaqumi et al and Amaura et al noted in their separate studies that CG is not a single disease but a unique pattern of renal parenchymal injury which may result from multitude of causes. 39,40. Accordingly, Mubarak and Kazi categorised the associated disorders of CG into infections, drug toxicity, autoimmune diseases, malignant tumours, genetic diseases, and ischemic conditions. 30 Therefore it is not unusual that we found CG lesions in HIV negative patients.

Tubulointerstitial lesions were not prominent in this study with the mean tubular atrophy being 11.1%. Most of the tubular lesions observed were associated with CG and included prominent protein reabsorbtion granules within the cytoplasm of the tubular epithelium and variable dilatation of the tubules with pale staining luminal precipitates. These findings are consistent reports of the morphologic changes of CG.

While 62.5% of patients with proliferative lesions presented with hypertension, only 36.4% of patients with non-proliferative lesions presented with hypertension. This is similar to the report from Kano which recorded prevalence of hypertension as 66.7% among MPGN patients as against the 37.5% in FSGS. 18 This may suggest that hypertension at presentation of renal disorder may point to an underlying proliferative glomerular lesion.

The mean duration of sickness prior to presentation to the clinic was 22.2 months. This is in keeping with the known trend of late presentation of patients in our environment, which often have dire consequences. Creating more awareness on recognising kidney symptoms early and presenting early will be helpful as much as providing health insurance that is generally accessible to members of the public. The latter will bring more people to the hospital as they will not pay out of their pockets.

***Conclusion.***

Renal biopsy practice is still inadequate in Port Harcourt. Although MPGN is the most common cause of NS in Port Harcourt children, collapsing glomerulopathy in HIV negative children also contributes significantly. There is need for increased utility of PRB in nephrology practice in order to optimize patient management in Port Harcourt.

***Acknowledgment***

We wish to acknowledge the ISN and IPNA as well as Dr Malcolm Lewis from United Kingdom and Profs. Felicia Eke and Ifeoma Anochie for their efforts in ensuring that the workshops during which the biopsies were taken, held. Appreciation also goes to Mrs Gift Oletu for her efforts in typing the manuscript.

***Table 1: shows gender and diagnoses distribution.***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Diagnosis** | **F** | **M** | **Total** | **%** |
| CG | 2 | 1 | 3 | 16% |
| FSGS | 1 | 3 | 4 | 21% |
| MCD | 1 | 3 | 4 | 21% |
| MP | 4 | 1 | 5 | 26% |
| MP+CG | 1 | 0 | 1 | 5% |
| MSP | 1 | 1 | 2 | 11% |
| **Grand Total** | **10** | **9** | 19 | 100% |

***Table 2: Shows gender distribution of SDNS and SRNS***

|  |  |  |  |
| --- | --- | --- | --- |
| Gender | SDNS  NO. (%) | SRNS  NO. (%) | TOTAL |
| F  M | 7 (63.3%)  4 (36.4%) | 3 (37.5%)  5 (62.5%) | 10  9 |
| Total | 11 (100%) | 8 (100%) | 19 (100%) |

***Table 3: Shows variation of SRNS and SDNS with age***

|  |  |  |  |
| --- | --- | --- | --- |
| **AGE RANGE** | **SDNS** | **SRNS** | **TOTAL** |
| 0-5 yrs. | 3 | 2 | 5 |
| 6-10 yrs. | 2 | 2 | 4 |
| 11-15 yrs. | 1 | 2 | 3 |
| ≥ 15 yrs. | 5 | 2 | 7 |
|  | 11 | 8 | 19 |

***Figure 1: showing age distribution of patients.***

***Figure 2 : Clinical indications for biopsy***

***Conflict Of Interest***

The authors declare no conflict of interest in this study.

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