Author’s response to reviews

Title: Trends In The Histopathology Of Childhood Nephrotic Syndrome In Ibadan Nigeria: Preponderance Of Idiopathic Focal Segmental Glomerulosclerosis

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Author’s response to reviews: see over
Ist Reviewer's Comments and Our Response

Title: Trends In The Histopathology Of Childhood Nephrotic Syndrome In Ibadan Nigeria: Preponderance Of Idiopathic Focal Segmental Glomerulosclerosis
Version: 3
Date: 20 July 2015
Reviewer: Larissa Kerecuk

Reviewer's report:
Thank you for your comments.

MAJOR REVISIONS
Authors need to define what they mean by 2 NS throughout.
We used 2° NS meaning secondary nephrotic syndrome. This has been revised to secondary NS wherever it appeared in the manuscript.

Authors need to include some discussion of fact that MCNS current pathophysiology including podocytes and genetic causes.
Concerning podocytopathies and genetics of these disorders we have expanded the discussion as follows:
“The recent discovery that two sequence variants in APOL1 (G1: rs73885319, G2: rs71785313) are more common in individuals of African descent (Yorubas of South Western Nigeria) compared with Europeans and that the disease associated alleles are more common in African Americans (AA) with FSGS compared with AA with no disease, may be important in our setting [45-47]. This is more so as most of our patients are of the Yoruba tribe. Recent reports in adult Nigerian populations have demonstrated APOL1 risk variants’ association with non-diabetic forms of CKD among Nigerians of Yoruba ethnicity in South-west Nigeria and also among the Igbos in South-east Nigeria [48,49].
The concept of podocytopathies as the unifying hypothesis for glomerular diseases [50] is presently widely propagated especially in relation to FSGS and MCNS. The complex interaction between environmental and genetic factors may then result in podocyte injuries of varying degrees. We hypothesize therefore that infectious agents acting on the genetically predisposed, probably those with APOL1 genetic mutation, may be responsible for the preponderance of FSGS seen in Ibadan, a Yoruba Land.”

The abstract, especially the methodology, is confusing and needs to be made clearer by explaining exactly when patients were biopsied and the various groups reviewed.
The dates and groups have been inserted in the abstract as follows:
Methodology: We reviewed our database and analyzed the renal biopsy findings in patients who were biopsied before treatment was administered [between 1997 and 2001] and those with mostly idiopathic steroid resistant NS (SRNS) and secondary NS, managed between 2006 and 2013. A comparative analysis of the findings from the present study was carried out with two previous reports from our Unit in the 1970s and early 1990s and also with reports from other Centres.
MINOR REVISIONS
Authors to ensure that all years are consistent in text - 1980s instead of 80s etc throughout text.
Authors to ensure that abbreviations are always defined for the first time they appear in text before using abbreviations.

We have ensured that all years are consistent in text - 1980s instead of 80s throughout text and that abbreviations are always defined for the first time they appear in text.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests
2nd Reviewer's Report and Our Comments
Title: Trends In The Histopathology Of Childhood Nephrotic Syndrome In Ibadan Nigeria: Preponderance Of Idiopathic Focal Segmental Glomerulosclerosis
Version: 3Date:10 September 2015
Reviewer: Manish D Sinha
Reviewer's report:
The study by Asinobi et al is an interesting paper, describing a relatively large series of children with nephrotic syndrome who underwent renal biopsy at the authors centre. Data presented is also compared with historical data from their own centre and with similar reports in the literature.
A total of 78 patients had successful biopsies done during the study period in children aged between 2 ó and 16years. In both pre-treatment biopsy era (1997-2001) and post-treatment biopsy era (2006-2013), focal segmental glomerulosclerosis (FSGS) predominated.

Thank you very much for your comments.
I have the following comments and concerns that need to be addressed:
1. Somewhat puzzling that the number of biopsies performed in the pre-treatment era are <50% of the number of biopsies in the post-treatment era. Please explain? If the policy was that all patients were biopsied before treatment there should be more in the earlier period as the authors also report an increase in the steroid responsive subjects.
The Reviewer’s observations are correct but please note that in the Pre-treatment era of this study, nephrology practice was extremely difficult in our country because of the downturn in our economy. A very few centres including ours could carry out biopsies. We lacked renal biopsy needles; expertise and many patients could not afford the cost of the procedure. Additionally, our practice was also punctuated by incessant industrial strike actions.
Without sounding immodest, we have the largest series of biopsies in both children and adults in Nigeria considering these periods of study.
Our practice has slightly improved but with out-of-pocket payments for investigations and treatment, we still cannot biopsy all the patients requiring biopsy at the present.
58 children were diagnosed with NS in the pre-treatment era while 106 children were treated in the post-treatment era. In our centre presently, combining our (staff) financial input and patients’ input for payment of the procedure, and baring industrial strike actions, our biopsy rate is about 70%.
The methodology has been amended to highlight the logistics limitations and the number of patients managed indicated in green. It read as follows:
Between 1997 and 2001, in accordance with the Unit protocol, all consecutive NS patients aged 16 years and below who had no contraindication were planned for biopsy before definitive treatment, in the absence of logistic hindrances (this period is referred to as the pre-treatment biopsy era).
In the first paragraph of the discussion, we have added the sentence below:
It should be noted that not all children that required biopsies had them because of financial constraints and lack of appropriate facilities.
2. What may be the reason for an increase in steroid unresponsive MCD subjects in the post treatment cohort?

It has been highlighted with green in the results and discussion sections of the manuscript. The others had secondary minimal change disease.

3. It is important that the authors give the reader some idea regarding number of subjects presenting with NS over the study periods. This would help understand some of the ‘discrepancies’ highlighted in earlier points.

58 children were diagnosed with NS in the pre-treatment era and 22 were biopsied while 106 children were treated in the post-treatment era and 56 biopsied. In our centre presently, combining our (staff) financial input and patients’ input for payment of the procedure, and baring industrial strike actions, our biopsy rate is about 70%. The sentence highlighted in green has been added to the methodology.

4. What proportion of subjects get biopsied – the relative numbers seem smaller than expected over study periods. Is it therefore correct to extend the findings to all children with NS in Nigeria.

Kindly refer to the explanations given earlier; we could not biopsy all the children that required biopsy because of lack of facilities and financial constraint.

Our results can be generalizable for Nigeria with regards to the histology of Steroid-resistant nephrotic syndrome but steroid sensitivity is so variable with some centres, notably the Lagos and Port-Harcourt Teaching Hospitals having up to 80% steroid sensitive patients. {Ladapo et al [15], Anochie et al [13], Obiagwu et al [39] }

5. What may be the reason for the gender differences? Please comment.

The gender difference in this cohort of nephrotic syndrome can only be explained by more females responding to steroid treatment which needs confirmation or the patient selection process. This aspect was not given prominence in the discussion.

6. Figure 1 (gender differences) should be removed.

Fig. 5 on gender comparison has been deleted.

Minor comments:
1. ‘in no distant time’ line 228/229 – please delete.
2. Suggest change ‘we also think’ to ‘it may also be possible that…’
3. Change ESRD to ESKD to keep with widely accepted terminology

The above corrections have been effected.
3rd Reviewer's report:
Title: Trends In The Histopathology Of Childhood Nephrotic Syndrome In Ibadan Nigeria: Preponderance Of Idiopathic Focal Segmental Glomerulosclerosis
Version: 3
Date: 7 September 2015
Reviewer: Neil Sebire
Reviewer's report:
This manuscript presents data from a series of cases of childhood nephrotic syndrome from Nigeria. The main findings of the study are that the underlying histopathological diagnoses have changed over several decades. The paper is therefore of potential interest to readers of the journal.

Thank you for your comments.

Overall, the manuscript is of suitable content with no major scientific issues given that it is a simple retrospective review of a large clinical series with all of the potential methodological issues that are inherent in such a study design, such as referral bias etc.
- Major Compulsory Revisions
My main specific suggestions would be whether the authors can provide more information regarding any specific FSGS subtypes, in particular features such as collapsing glomerulopathy and HIV associated nephropathy within this context.

The discussion has been expanded and the whole paragraph reads as follows:
The high proportion of FSGS in our setting may explain the high incidence of steroid resistance among children and adolescents with NS. With regards to the specific types of FSGS, these patients who were majorly steroid-resistant showed the "Not-otherwise specified FSGS" and this was not surprising. It is possible that patients with the "tip lesion" type would have responded to steroid therapy and therefore not biopsied. Only a case of collapsing FSGS was seen. We did not encounter many children with HIV requiring renal biopsy because as soon as the highly active antiretroviral therapy (HAART), the proteinuria resolved. Out of the five patients with HIV and massive proteinuria seen during the latter years, two were biopsied; one had HIVAN and the other Membranous nephropathy. Other renal diseases encountered were AKI, CKD but not many with the NS as documented in our previous study [43].

- Minor Essential Revisions
I would remove the graph of sex distribution instead replace it with the graph showing the data from tables 1 and 2 which would therefore graphically demonstrate the histopathological patterns found, these being the main findings of this study.

The graph on sex distribution has been deleted. We have converted Tables 1 and 2 to figures but left the table 2 for your comparison with figure 2. Other corrections have been effected and highlighted in green.

Otherwise, the overall manuscript is acceptable although will require some significant editorial input throughout in terms of the language and style used but the overall content
is acceptable.  Overall therefore I have no major scientific reasons why the study not be published following these suggested changes.  
Level of interest: An article whose findings are important to those with closely related research interests  
Quality of written English: Needs some language corrections before being published.  
Statistical review: No, the manuscript does not need to be seen by a statistician.  
Declaration of competing interests:  
'I declare that I have no competing interests'