University of Zambia

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THE CLINICAL CHARACTERISTICS AND HISTOLOGICAL SUBTYPES OF NEPHROTIC SYNDROME IN PAEDIATRIC PATIENTS AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA

BY

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(BSc. HB, MBChB)
A Dissertation Submitted to the University Of Zambia in Partial Fulfilment of the Requirements of the Degree of Master of Medicine in Paediatrics and Child Health

THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

2015
DECLARATION

I declare that this dissertation is my own work. It is being submitted for the Master of Medicine in paediatrics and child health at the University of Zambia, Lusaka. It has not been submitted before for any degree or examination at this or any other University.

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ABSTRACT

BACKGROUND: Nephrotic syndrome (NS) and glomerulonephritis are the commonest glomerular diseases seen at the University Teaching Hospital (UTH), Lusaka, in the department of Paediatrics and Child Health. [1] Nephrotic syndrome commonly presents with hypoalbuminaemia, oedema and hyperlipidaemia. Little is known about the clinical characteristics and histological patterns Zambian children. This study investigated the clinical characteristics and histological subtypes of NS patients presenting to the Department of Paediatrics and Child Health, at the University Teaching Hospital, in Lusaka, Zambia.

METHODOLOGY: A non-randomized prospective study of consecutive cases of Zambian children with nephrotic syndrome was conducted between August 2014 and March 2015.

RESULTS: Thirteen participants were enrolled in this study. Median NS onset age was 9.25 years (2.0-15.0). Male: female ratio was 1:1.16. Out of the 13 participants, 10 had atypical features such as haematuria and hypertension in addition to the classic features of NS. The histopathologic lesions were MCD (4/13 participants), FSGS (4/13 participants) and immune complex mediated Membranous Nephropathy (1/13 participants). Histology reports for the other 4 participants were inconclusive. Two patients with FSGS had the perihilar variant while the other two had the not otherwise specified (NOS) variant. Two participants attained remission during the period of the study and they were both early responders with one having MCD and the other having the perihilar variant of FSGS.

CONCLUSION: Most of our participants had atypical presentation (76.9%) i.e. presented with haematuria or hypertension, or both, in addition to the classic clinical characteristics. The predominant lesions were non-MCD with FSGS accounting for 4 and immune complex induced Membranous Nephropathy for 1 out of the 9 patients with biopsy reports. Out of the 13 children, only 2 attained remission during the 7 month period showing that MCD in our participants did not respond well to steroid therapy.
DEDICATION

I dedicate this work to my mother and father for providing me with the support and parental guidance throughout my education, for without them I would not have pulled through this journey. Above all I am indebted to my ever loving wife, Tionenji Zulu Mashanga and our son Chikondi for supporting me throughout this research and career.

To our Heavenly Father- I am so grateful to our Father in heaven for the gift of life and the strength that he has constantly given me. Without you Lord, I wouldn’t be here.
ACKNOWLEDGEMENTS

My sincere gratitude goes to my supervisors Prof Mary Shilalukey Ngoma, Dr Veronica Mulenga, and Dr Aggrey Mweemba who corrected, supported and encouraged me while making this work interesting all the way through it. I would also like to thank Dr Noor and Dr Charles Mutemba, the renal physicians without whom I would not have managed to do the renal biopsies. Last but not the least I would like to thank all the participants in the study, for without them this study would not have been possible.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>FGS</td>
<td>Focal and Global glomerulosclerosis</td>
</tr>
<tr>
<td>FRNS</td>
<td>Frequently Relapsing Nephrotic Syndrome</td>
</tr>
<tr>
<td>FSGS</td>
<td>Focal Segmental Glomerulosclerosis</td>
</tr>
<tr>
<td>INS</td>
<td>Idiopathic Nephrotic Syndrome</td>
</tr>
<tr>
<td>ISKDC</td>
<td>International Study of Kidney Disease in Children</td>
</tr>
<tr>
<td>MCD</td>
<td>Minimal Change Disease</td>
</tr>
<tr>
<td>MCNS</td>
<td>Minimal Change Nephrotic Syndrome</td>
</tr>
<tr>
<td>MGN</td>
<td>Membranous Glomerulonephritis</td>
</tr>
<tr>
<td>MN</td>
<td>Membranous Nephropathy</td>
</tr>
<tr>
<td>MPGN</td>
<td>Membranoproliferative Glomerulonephritis</td>
</tr>
<tr>
<td>NS</td>
<td>Nephrotic Syndrome</td>
</tr>
<tr>
<td>SDNS</td>
<td>Steroid Dependant Nephrotic Syndrome</td>
</tr>
<tr>
<td>SRNS</td>
<td>Steroid Resistant Nephrotic Syndrome</td>
</tr>
<tr>
<td>SSNS</td>
<td>Steroid Sensitive Nephrotic Syndrome</td>
</tr>
<tr>
<td>UTH</td>
<td>University Teaching Hospital</td>
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</tbody>
</table>
CHAPTER ONE

1.0. INTRODUCTION
Nephrotic syndrome and glomerulonephritis are the commonest glomerular diseases seen at the University Teaching Hospital (UTH), in Lusaka, in the department of Paediatrics and Child Health.\[1\] Nephrotic syndrome commonly presents with hypoalbuminaemia, oedema and hyperlipidaemia but little is known on the histological patterns of the disease in Zambian children.

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome (INS), which based on the histological findings on renal biopsy, is further classified into minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), membranous glomerulonephritis (MGN), and focal and global glomerulosclerosis (FGS).\[2\]

The International Study of Kidney Disease in children (ISKDC) showed that the majority of white children in North America, Europe and Asia with INS have minimal change nephrotic syndrome (MCNS) which responds to corticosteroid treatment and that a kidney biopsy is not indicated.\[3\] Based on these findings empiric corticosteroid treatment was recommended, without need of performing a kidney biopsy.\[4\] These recommendations have been implemented worldwide as standard of care for the past 40 years but may not be applicable to other settings with a predominance of black patients,\[4, 5\] like Zambia.

The initial treatment for new-onset nephrotic syndrome is prednisolone given at 60 mg/m\(^2\)/day (maximum 80 mg/d) for 4 to 8 weeks, followed by 40 mg/m\(^2\) every other day for another 4 to 8 weeks, and then a gradual taper until it is discontinued.\[5, 6\] In patients with (Frequently Relapsing NS) and SDNS (Steroid Resistant NS), alternative agents with potential steroid sparing effects are often used, including cyclophosphamide, levamisole, cyclosporine, tacrolimus, and mycophenolate mofetil. In patients with SRNS (Steroid Resistant NS), however, the most commonly used agents include cyclosporine, tacrolimus, high dose intravenous methylprednisolone, and mycophenolate mofetil (MMF), although the efficacy of almost all these agents is lower in these patients compared with FRNS or SDNS patients. Most of these steroid sparing drugs are not readily available in resource constrained countries such as ours.
In most parts of the world NS is dominated by MCNS (>90%), with a predictable and gratifying response to steroids and an excellent long-term prognosis.\textsuperscript{[7]} However studies among black children show paucity of MCNS, steroid resistance (SR) in the majority, a less satisfactory outcome and an identifiable causative agent in many.\textsuperscript{[8–10]}

Infectious agents may be an important cause of NS in African children. The epidemiology of infectious agents differs substantially as one traverses Africa from the north to the South.\textsuperscript{[11]} Often there is a strong correlation between renal histology and microbial aetiology, and thus the pathology of NS has a strong regional bias. Infections such as malaria, schistosomiasis, hepatitis B and HIV have been suggested as major causes of nephrotic syndrome (NS) in African children.\textsuperscript{[12]}

MCNS and FSGS are the commonest lesions and often have a similar presentation, but differentiation between the two is of major clinical relevance to both the patient and the physician in assessing long-term prognosis and treatment options.\textsuperscript{[13]} The two entities not only differ in their glomerular histology and response to corticosteroid therapy, but most importantly in the tendency for FSGS to progress to end-stage renal failure, which hardly occurs in MCNS.\textsuperscript{[2]}Studies done in different parts of the world including Africa have shown an increase in FSGS especially among blacks.\textsuperscript{[14]} This means that NS in blacks may actually pose a serious management problem in developing countries where management protocols are adapted from the western world.

To date there have been no studies done in Zambia, both in adults and children, to document the clinical characteristics and histological subtypes of NS. This study therefore sought to investigate clinical characteristics and histological subtypes of NS in paediatric patients presenting to department of Paediatrics and Child Health, the UTH, Lusaka, Zambia.
CHAPTER TWO

2.0. LITERATURE REVIEW

The annual incidence of NS in most countries in the Western Hemisphere is estimated to range from 2 to 7 new cases per 100,000 children\(^5,13,15-17\) and the prevalence is about 12 to 16 cases per 100,000 children.\(^5\) Compared to developed countries the incidence of NS in developing countries is 15 to 50 fold higher.\(^18\) There is a male preponderance among young children, with a ratio of 2:1, although this gender disparity disappears by adolescence, making the incidence in adolescents and adults equal among males and females.\(^6,15,19-21\)

The most common age of presentation is 2 years, and 70% to 80% of cases occur in children younger than 6 years old.\(^5,15\) To some extent age also predicts the histologic lesion associated with nephrotic syndrome. Children diagnosed before age 6 represented 79.6% of those with MCNS compared with 50% of those with FSGS and only 2.6% of those with MPGN.\(^3\) Excluding the first year of life the likelihood of having MCNS decreases with increasing age, whereas the likelihood of having the less favourable diagnosis of FSGS or MPGN increases.\(^3,23\)

The incidence and the histologic patterns of nephrotic syndrome are also affected by geographic location and ethnic origin. In a report from the United Kingdom, idiopathic nephrotic syndrome was found to be 6 times more common in children of Asian descent living in the United Kingdom than among their European counterparts.\(^23\) In the United States, a review of children diagnosed with nephrotic syndrome in Houston, Texas, revealed that the distribution of patients closely resembled the ethnic composition of the surrounding community.\(^19\) These data in conjunction with data from African countries seem to suggest that the interaction of genetic and environmental factors is important in the pathogenesis of nephrotic syndrome. However, race appears to have an important impact on the histologic lesion associated with nephrotic syndrome. In this same study the authors found that although only 11% of Hispanic and 18% of Caucasian patients with nephrotic syndrome had FSGS, 47% of African American children had this less favourable diagnosis.\(^19\)
Though the ISKDC showed that MCNS is the commonest histopathological lesion seen in children with INS, this may not be true in the African population. MCNS is uncommon in Africa except in Arab African, Indian and white South African children. Oluwo et al showed that eight of eleven renal biopsy proven reports INS in Africa had other forms of glomerular disease other than MCNS as predominant lesions. In a recent study done in Nigeria, the prevalence of non-MCNS was very high with MPGN (44.4%) and FSGS (25.9%) being the dominant pathology types.

The histologic lesion associated with nephrotic syndrome determines the response to treatment. In a multicentre ISKDC study, 93% of those with MCNS compared with only 30% of those with FSGS and 7% of those with MPGN, attained remission following an initial 8 week course with prednisolone. In addition to histology, response to steroids also varies with geographic location and ethnicity. Whereas 80% of children in western countries will be steroid responsive, studies from Zambia, South Africa, Nigeria, and more recently Ghana show that only 9% to 50% of children with nephrotic syndrome are steroid responsive. Failure to respond to steroid treatment is associated with a risk of developing progressive renal failure later in life. In a multicentre evaluation of 75 children with FSGS, it was found that within 5 years after diagnosis, 21% had developed ESRD, 23% had developed CKD, and 37% had developed persistent proteinuria, whereas only 11% remained in remission. Thus once a child is diagnosed with FSGS, the risk for development of CKD or ESRD within 5 years is almost 50%. These studies provide some evidence that pre-treatment renal biopsy maybe necessary to guide diagnosis and treatment of NS in black African children. 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. Steroid-sparing agents include drugs such as cyclophosphamide, chlorambucil, cyclosporine, rituximab and levamisole and are used in SDNS, FRNS and SRNS.

A study done at the University Teaching Hospital, in Lusaka, Zambia, by Ngoma et al, revealed that half of the children presenting for tertiary care were steroid responsive suggesting minimal change nephropathy in Zambian children. This study also showed that in a resource constrained environment like ours where there is limited access to renal biopsy, steroid responsiveness remained the most important predictor of the outcome of
NS. However the need to investigate patients adequately including doing renal biopsies to guide diagnosis and therapy was emphasized.

Several studies show that there has been an increasing incidence of focal segmental glomerulosclerosis (FSGS) in children and adults with idiopathic nephrotic syndrome (INS). This increase has been observed particularly in certain racial groups and ethnic populations. Several studies suggest that the incidence of FSGS is increasing particularly in the black population.

Our study sought to describe the histological subtypes and clinical characteristics of NS in children presenting to the department of Paediatrics and Child Health at the University Teaching Hospital, in Lusaka, Zambia.
CHAPTER THREE

3.1. STATEMENT OF THE PROBLEM
In a study done in Zambia, at the University Teaching Hospital, on children presenting with NS only 50% of children had an initial response to steroid treatment. No follow up study has been done to describe the histopathological pattern of NS in these children. Like most resource constrained countries, Zambia uses treatment protocols adapted from the developed world. This study will provide insight into the histological sub-types common in children seen at UTH.

3.2. STUDY JUSTIFICATION
It has been documented that knowing the histological sub-types of NS in children has a great bearing on treatment modality and outcome. Therefore documenting histopathological sub-types of NS will guide in the development of protocols for effective treatment strategies and therefore prevention of chronic renal disease and end stage renal disease (ESRD) in children with NS seen at UTH.

3.3. HYPOTHESIS
Focal segmental glomerulosclerosis (FSGS) accounts for about 50% of lesions among children presenting with Nephrotic Syndrome to the paediatric department at the University Teaching Hospital, Lusaka.

3.4. STUDY QUESTIONS
1. What are the common histological subtypes of Nephrotic Syndrome in paediatric patients presenting to UTH?
2. What are the common clinical characteristics found in children with Nephrotic Syndrome at UTH?
3.5.OBJECTIVES

3.5.1. MAIN OBJECTIVE
To describe the histological subtypes and the clinical characteristics of Nephrotic syndrome in paediatric patients at the University Teaching Hospital.

3.5.2. SPECIFIC OBJECTIVES:
1. To describe the histopathological sub-types of NS in children presenting to UTH.
2. To describe the clinical characteristics associated with NS in children presenting to UTH.
3. To determine the proportion of children with different histological sub-types of Nephrotic Syndrome in children presenting with NS at UTH
4. To describe treatment response to steroids in children with NS presenting to UTH
CHAPTER FOUR

4.0 MATERIALS AND METHODS

4.1. STUDY DESIGN
This was a cross sectional study. Data was collected between August 2014 and March 2015.

4.2. STUDY SITE
The study was conducted at the University Teaching Hospital, Department of Paediatrics and Child Health. This UTH is the biggest referral hospital in Zambia offering tertiary care. It handles approximately 32,000 to 36,000 children annually. Of these, 12,000 to 16,000 are re-attendances. Common disease conditions include malaria, malnutrition, respiratory tract infections, tuberculosis, diarrheal disease and HIV disease. Renal disease constitutes less than 1%. [1]

4.3. STUDY POPULATION
All patients with a clinical diagnosis of nephrotic syndrome (NS) were eligible for recruitment. These included new and old patients. In this study, NS was defined as a constellation of proteinuria greater than 2+ on a urine dipstick test, hypoalbuminaemia of less than 25g/L and oedema. Children with haematuria in addition to the criteria for NS were also included.

4.4. ELIGIBILITY

4.4.1. Inclusion Criteria
All children with the diagnosis of NS aged 2-16 years whose guardians consented and provided written consent and/or assent.

4.4.2. Exclusion Criteria
- Declined consent or assent
- Liver disease
- Sickle cell disease
- Diabetes Mellitus
- Single kidney
- CKD with creatinine > 250
- Any other bleeding disorder
- HIV Infection
- Syphilis
- Hepatitis B or C
- Schistosomiasis
- History of severe malaria or presence of malaria at the time of diagnosis

4.5. Sample size
All eligible children being followed up in the nephrology clinic and/or newly diagnosed patients were invited to participate in the study.

Our aim was to enrol a minimum of 25 patients which would have allowed sufficient power to identify a 50% prevalence of FSGS with an error margin of ± 14%. However, only 13 patients were enrolled during this period as these were the only ones who met the criteria.

4.6. Sampling
The convenient sampling method was used. All patients, being followed up in the children’s nephrology clinic, who met the eligibility criteria, were included in the study as well as newly diagnosed patients being managed as in-patients.

4.7. Procedures
Guardians/Parents of all children with the diagnosis or probable diagnosis of NS were approached to enter the study. Information about the study was given to the guardians and all children whose guardians gave consent were screened for the study.

A detailed history was taken by the researcher at the screening points. History included patient demographics, presenting complaints, past medical and drug history.

A thorough physical examination was done. Urinalysis was done and vitals such as body temperature, pulse, respiratory rates and blood pressure were obtained.

Participants who met the criteria and consented to entry were recruited.
The following investigations were done:
- Serum albumin, serum cholesterol
- Serum creatinine, Urea and Electrolytes
- Liver Function Tests
- FBC
- Solubility test
- INR and bleeding time
- Hepatitis BsAg and C serology
- Stool microscopy
- HIV antibody test after pre-test counselling by qualified counsellors

A pre-biopsy abdominal ultrasound scan was done by an experienced nephrologist on the participants who met the criteria for renal biopsy. Contraindications to renal biopsy included:

- Bleeding disorders
- Single kidney or small kidney for age
- Liver disease
- Platelets 150 and below
- Patients with uncontrolled hypertension
- Established chronic renal disease with creatinine >250

4.7.1. Renal biopsy

Renal biopsy was the hallmark of this study. It was done in the adult renal unit at UTH after adequate screening and preparation of patients in order to minimize complications.

All surgical preliminaries were observed before, during and after the procedure including sterile preparations, anaesthesia and post-operative monitoring of vital signs such as pulse rate and blood pressure. After preparing the patient, renal biopsy was done under ultrasound guidance with the patient lying in the prone position. The procedure was performed by the researcher and a qualified nephrologist. After biopsy, the specimen was placed in a container containing formaldehyde and sent to the histology laboratory where the glomerular lesions were defined along standard diagnostic light microscopy lines by a qualified pathologist and a report submitted to the researcher. Five or more glomeruli per renal tissue specimen were regarded as adequate for reporting. [48]
Following the biopsy, the patient was asked to lie flat on the back for 4–6 hours to minimise the risk of bleeding. Blood pressure, pulse rate and urine were monitored frequently to ensure the patient did not suffer any complications of bleeding. Pain was controlled with paracetamol.

4.8. Operational Definitions

1. **Nephrotic Syndrome**: Diagnosis of nephrotic syndrome requires the presence of oedema, massive proteinuria (>40 mg/m²/hr or a urine protein/creatinine ratio >2.0 mg/mg), and hypoalbuminemia (<2.5 g/dL).\(^5, 52\) In this study, dipstick proteinuria of 3+ or more was considered significant.

2. **Remission**: Remission is characterized by a marked reduction in proteinuria (urine albumin dipstick of negative to trace for 3 consecutive days) in association with resolution of oedema and normalization of serum albumin to at least 3.5 g/dL.\(^5, 52\)

3. **Relapse**: Relapse is defined as recurrence of massive proteinuria (urine albumin dipstick ≥2+ on 3 consecutive days), most often in association with recurrence of oedema.\(^5, 52\)


5. **Steroid-Resistant Nephrotic Syndrome (SRNS)**: Patients who fail to attain remission after 8 weeks of corticosteroid treatment.\(^5, 52\)

6. **Steroid-Dependent Nephrotic Syndrome (SDNS)**: These are patients who respond to initial corticosteroid treatment by going into complete remission but develop a relapse either while still receiving steroids or within 2 weeks of discontinuation of treatment following a steroid taper.

7. **Infrequent Relapse**: having 3 or less relapses in any 12 month period.

8. **Frequent Relapsing Nephrotic Syndrome (FRNS)**: Two or more relapses within 6 months of initial response or four or more relapses within any 12 month period.
4.9. Data Management
- Data was collected and entered by the researcher himself.
- A standardized data entry questionnaire for each study participant was used for data collection. No personal details that may help identify participants appeared on the form. Data was entered on an Epi Info database.
- Routine monitoring of data collection tools by means of once daily spot checks for completeness and errors was carried out.

4.10. Statistical Analysis
Descriptive statistics used comprised mean, standard deviation (SD), median, percentages, and proportions. These were presented as tables and charts.

4.11. Ethical Issues
Ethical clearance was sought from the Research Ethics Committee (ERES), Ref.no 2014-May-043. Permission to carry out the study was sought from the University Teaching Hospital, and the Department of Paediatrics and Child Health, and was granted.

The purpose and procedures of the study were fully explained and a written informed consent/ascent obtained from the guardian/parent and participant where possible. It was emphasized that participation in the study was purely voluntary and that participants could withdraw from the study at any point. The risks and benefits were fully explained to the participants as described in the consent form.

Patient results were strictly confidential. All data entry forms were identified by coded numbers only. The data entry sheets were locked in a secure cabinet and all electronic entries were password protected.

Participants in need of treatment or follow up were stabilized and referred appropriately. Recommendations have been made to the relevant authorities.
CHAPTER FIVE

5.0. RESULTS AND DATA ANALYSIS

The study was designed to enrol 25 participants with the aim of coming up with a histologic diagnosis. Thirteen (13) participants were enrolled into the study and had renal biopsies done. Out of the 13, 7 (53.8%) were female children and 6 (46.2%) were male children with no statistical difference in sex proportions (P= 0.78) as shown in table 1. The median age at diagnosis of NS and enrolment into the study was 9.5 years and 12 years respectively as shown in table 1.

Table 1: Demographic and Baseline Characteristics of the Patients (N=13)

<table>
<thead>
<tr>
<th>Demographic and baseline clinical characteristics</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>7 (53.8%)</td>
</tr>
<tr>
<td>Male(%)</td>
<td>6 (46.2%)</td>
</tr>
<tr>
<td>Male to Female ratio</td>
<td>1:1.16</td>
</tr>
<tr>
<td>Mean age at Diagnosis (range)</td>
<td>9.25±4.063 (2-15)</td>
</tr>
<tr>
<td>Mean age at Enrolment (range)</td>
<td>11.54±3.332 (5-15)</td>
</tr>
<tr>
<td>Height (range)</td>
<td>1.53 (1.06-1.74)</td>
</tr>
<tr>
<td>Weight (range)</td>
<td>40 (17-73)</td>
</tr>
<tr>
<td>Mean Systolic Blood Pressure (range)</td>
<td>113 (90-140)</td>
</tr>
<tr>
<td>Mean Diastolic Blood Pressure (range)</td>
<td>67 (60-90)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.96 (10-14)</td>
</tr>
<tr>
<td>Mean Serum Albumin (g/L)</td>
<td>16.2</td>
</tr>
<tr>
<td>Mean Serum Cholesterol (mmol/L)</td>
<td>8.2±2.16</td>
</tr>
<tr>
<td>Mean Serum Urea (mmol/L)</td>
<td>3.5 (1.5-6)</td>
</tr>
<tr>
<td>Mean serum Creatinine (µmol/L)</td>
<td>38.53 (18-61)</td>
</tr>
<tr>
<td>Mean eGFR (ml/min/1.73m²)</td>
<td>130.3 (97.7-235.0)</td>
</tr>
<tr>
<td>Haematuria (%)</td>
<td>8 (61.5%)</td>
</tr>
<tr>
<td>Proteinuria (3+ by dipstick urinalysis)</td>
<td>13 (100%)</td>
</tr>
</tbody>
</table>

Age was measured in years; Height measured in meters; Weight measured in kilograms (Kg); Blood Pressure measured in millimeters of mercury (mmHg); Pulse rate measured as beats per minute eGFR: estimated GFR; mmol/L: millimoles per litre; µmol/L: micromoles per litre; Haematuria: dipstick urinalysis of 1+ or more was considered significant
All participants recruited in this study were of the black race and none of them were found with diabetes mellitus, sickle cell disease, hepatitis B/C, HIV, Malaria, or Schistosomiasis. All the 13 children were analysed as per study protocol. Other laboratory characteristics are as shown in table 1.

**Figure 1: Newly Diagnosed Vs Known patients with Nephrotic Syndrome**

![Pie chart showing distribution of newly diagnosed and known patients with nephrotic syndrome]

Seven (54%) of the enrolled were newly diagnosed NS patients whereas the remainder were already known NS patients who were being followed up in the nephrology clinic (figure 1). Of the 6 known NS patients, 5 children reported less than 3 relapses, and one child reported 4 relapses in the 12 months preceding enrolment.

All the 13 children enrolled into the study had a renal biopsy done out of whom 9 had their reports available and the other 4 reports were inconclusive as shown in fig 2.
Figure 2: Histology Reports (N=13)

Four (4) of the patients had MCD. Three of these patients had atypical presentation with one having haematuria only and the other two with both haematuria and hypertension (Table 2). Five (5) children had non-MCD, four (4) of whom had FSGS and one (1) had immune complex mediated MN. All the four children with FSGS had atypical presentation in addition to the classic parameters; with one having haematuria only, one with hypertension only, and the other two with both haematuria and hypertension. The patient with immune complex mediated MN was the youngest with the age at diagnosis being 2 years and he had both hypertension and haematuria at presentation with primary steroid resistance. Haematuria was present in 2 patients whose biopsy reports were inconclusive and were both on antihypertensive at the time of recruitment into the study.

MCD: Minimal Change Disease
Table 2: Clinical Characteristics and Histological Subtypes

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>MCD</th>
<th>FSGS</th>
<th>MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematuria</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HTN</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Haematuria and HTN</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Primary Steroid Resistance</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

HTN-Hypertension, MCD-Minimal Change Disease (Minimal Change Nephrotic Syndrome), FSGS-Focal and Segmental Glomerulosclerosis, MN-Membranous Nephropathy

All the patients recruited in this study were followed up in the clinic and their response to steroid therapy noted. Two of the seven newly diagnosed had gone attainned remission during this period which lasted seven months. Of the two, one had MCD and the other one had FSGS. The other five newly diagnosed were all steroid resistant. Three of the four patients whose reports were not available were all steroid resistant with the remaining one being steroid dependant on both Levamisole and prednisolone.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of glomeruli represented in Biopsy Specimen</th>
<th>Corticomedullary junction represented</th>
<th>Histological conclusion</th>
<th>% global sclerosed</th>
<th>Tubulointerstitial involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/6</td>
<td>23</td>
<td>Absent</td>
<td>MCD</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• probable FSGS with hyalinosis due to absence of corticomedullary junction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/11</td>
<td>14</td>
<td>Present</td>
<td>MCD</td>
<td>14</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• probable FSGS with hyalinosis due to presence of a focus of chronic interstitial nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/12</td>
<td>39</td>
<td>Present</td>
<td>MCD</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>F/15</td>
<td>14</td>
<td>Present</td>
<td>MCD</td>
<td>7</td>
<td>Normal</td>
</tr>
<tr>
<td>F/12</td>
<td>8</td>
<td>Present</td>
<td>Primary FSGS with Hyalinosis</td>
<td>50</td>
<td>Mild</td>
</tr>
<tr>
<td>F/14</td>
<td>26</td>
<td>Present</td>
<td>Primary FSGS with Hyalinosis</td>
<td>12</td>
<td>Mild</td>
</tr>
<tr>
<td>M/14</td>
<td>13</td>
<td>Absent</td>
<td>Primary FSGS with Hyalinosis</td>
<td>31</td>
<td>Moderate to Severe</td>
</tr>
<tr>
<td>M/15</td>
<td>50</td>
<td>Absent</td>
<td>Primary FSGS with Hyalinosis</td>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>M/5</td>
<td>6</td>
<td>Absent</td>
<td>Immune complex mediated diffuse membranous nephropathy with stage 1-2 phase changes, accompanied by mesangiopathic alterations</td>
<td>Nil</td>
<td>Mild</td>
</tr>
</tbody>
</table>

*FSGS: Focal and Segmental Glomerulosclerosis; MCD: Minimal Change Disease*
Table 3 shows the histological description for each patient including: number of glomeruli represented per biopsy and tubulo-interstitial involvement. The number of glomeruli ranged from six to 50. In four patients, the corticomedullary junction was not represented. There was a mild interstitial nephritis in five patients, three had no interstitial involvement and one patient had moderate to severe interstitial nephritis. Global sclerosis was present in seven patients and ranged from 2% to 50%.

Table 4: FSGS Description

<table>
<thead>
<tr>
<th>Patient</th>
<th>% of Glomeruli involved</th>
<th>% Global sclerosis</th>
<th>FSGS Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/12</td>
<td>50</td>
<td>50</td>
<td>Perihilar</td>
</tr>
<tr>
<td>F/14</td>
<td>31</td>
<td>12</td>
<td>Perihilar</td>
</tr>
<tr>
<td>M/14</td>
<td>31</td>
<td>31</td>
<td>NOS</td>
</tr>
<tr>
<td>M/15</td>
<td>66</td>
<td>2</td>
<td>NOS</td>
</tr>
</tbody>
</table>

NOS: Not Otherwise Specified

Table 4 shows the description for FSGS and the location and type of the lesion. All lesions were located in the periphery with two patients also having perihilar involvement. Percentage of glomeruli with focal and segmental glomerulosclerosing lesions ranged from 31% to 66% as shown in table 4.
Chapter Six

6.0. Discussion

This is the first descriptive study on NS done in Zambia and only a few participants were enrolled.

6.1. Clinical Characteristics

There was no significant difference in the proportion of male to female participants (1:1.16). Most of our patients were above the age of 6 years old at diagnosis which is outside the age for typical presentation (2 years to 6 years).\(^{[5, 15]}\) The median age at onset in this study was 9.5 years which is not very different from that observed in the study done by Olowu et al in Nigeria (median=7.1 years [N=78])\(^{[39]}\) and this varies significantly with onset age in Asia, Europe and North America where most of the cases occur under the age of 6 years\(^{[3, 51, 52]}\) due to MCD predominance.

Ten out of the thirteen patients enrolled in this study had atypical presentation at diagnosis (table 1). Haematuria was present in 8/13 patients (61.5%) and hypertension was present in 5 patients (38%). Only 3/13 patients did not have either haematuria or hypertension. This is in agreement with some other studies done elsewhere which have shown that NS in black children is usually atypical.\(^{[8-10]}\)

The high frequency of atypical presentation in this study (i.e. haematuria and hypertension) reflects non-MCD predominance. We can therefore infer, from the clinical presentation, that the other 4 patients without biopsy reports are likely to have non-MCD than MCD. Only one child out of the four did not have either haematuria or hypertension.

6.2. Histological Sub-types

MCD was found in 4/9 patients (44.4%) in this study. Two of them were diagnosed at 4 years and 6 years old respectively. The other two were diagnosed at 11 years and 15 years respectively. FSGS was found in 4/9 patients (44.4%). All patients with FSGS were above the age of 6 years at diagnosis. The youngest was 11 years old at diagnosis and the other 3 were 12, 14 and 14.5 years respectively and only one showed initial steroid response (the 12 year old) whereas the others showed primary steroid resistance.
The youngest patient in this study had immune complex mediated Membranous Nephropathy. He presented at 2 years of age and currently being managed as SRNS with good response to cyclosporine. This patient would have benefitted from immunoflourecent studies.

The lesions observed in this study may have been influenced by age at onset as most of our patients were above the age of 6 years and therefore less likely to have MCD.\textsuperscript{[3, 22]} It is also important to note that 3 out of 4 patients with MCD had atypical presentation thereby making it very difficult to distinguish MCD in older children from non-MCD without a renal biopsy (\textit{table 3}).

6.3. FSGS VARIANTS
Four patients in this study had FSGS. Two of the patients had the perihilar variant while the other 2 had the not otherwise specified (NOS) variant. Classically, the tip lesion has been considered the most responsive to steroid therapy while the collapsing variant has been thought to be steroid-resistant and associated with a more aggressive clinical course. This has been largely validated by multiple series from diverse ethnic and demographic groups.\textsuperscript{[54]} The tip lesion is the commonest in whites whereas the collapsing lesion is said to be more common in blacks.\textsuperscript{[54]} The prognostic significance of perihilar and NOS variants has not yet been determined. Our patients had the perihilar and NOS variants. Only one of the 4 patients went into remission during the period of the study and had the perihilar variant with no tubulo-interstitial involvement and no globally sclerosed glomeruli.

6.4. RESPONSE TO STEROID THERAPY
All patients in this study were followed up in the nephrology clinic and their response to steroid therapy observed. Seven out of the nine patients (77.8\%) with biopsy reports showed primary steroid resistance. Three had MCD (33.3\%); and 3 had FSGS (33.3\%); and the other one was the patient in who had immune complex mediated Membranous Nephropathy (\textit{table 2}). Two patients attained remission within 4 weeks of steroid initiation. One of the two had MCD and the other had FSGS. Regarding the other 4 patients with inconclusive histology reports, 3 were steroid resistant and one was steroid dependant.
6.5. ADEQUACY OF BIOPSIES

The minimum number of glomeruli for a renal biopsy specimen to be adequate for light microscopy is 5. In our study, the glomeruli ranged from 6 to 50 (table 3). The patient with the least glomeruli was the patient with immune complex mediated membranous nephropathy.

The corticomedullary junction was absent in 4/9 specimens with only one of these showing MCD. This patient however had adequate glomeruli (table 3) and most likely adequate to make the diagnosis of MCD. The pathologist however concluded that it was MCD but could also be an unsampled FSGS with hyalinosis since the corticomedullary junction was not represented. Another patient had 14 glomeruli represented in the specimen with 14% showing global glomerulosclerosis and the pathologist concluded that it was MCD but there was a possibility of unsampled FSGS with hyalinosis in the adjacent unsampled glomeruli due to the presence of a focus of chronic interstitial nephritis. Going by these results, and the clinical presentation, it is possible that these two patients had FSGS. The extent of lesions varies in different portions of the kidney, ranging from normal unaffected glomerulus to segmental sclerosis and, eventually, global glomerulosclerosis as the disease progresses. The focal nature of the glomerulosclerosis means that some mild cases of FSGS will be missed on renal biopsy due to sampling error and will be misclassified as minimal change disease. Immunofluorescence studies would have been very helpful in classifying these lesions better.

6.6. IMPLICATIONS OF THE FINDINGS

The findings in this study have demonstrated the need to describe the histological subtypes in the patients presenting to the department with NS. Despite the sample size being small, we observed that 76.9% of the patients we saw during this period (August 2014 to March 2015) had atypical NS and that most of them did not respond very well to steroid therapy. We also observed that it is difficult to distinguish MCD and non-MCD based on clinical characteristics and that a pre-treatment renal biopsy should be recommended for all patients with NS. However, a larger study would be more informative.
6.7. **LIMITATIONS**

1. The small sample size limits generalisability to the rest of the country or the region.

2. The time frame for this study was too short to give us adequate numbers. There is need to do a similar study but over a period not less than 2 years in order to capture more patients and follow them up to look at their response to therapy.

3. Light microscopy alone was not adequate to give more detail regarding the lesions. Immunofluorescence studies would have given more detail, however, due to financial constraints, this was not possible.
CHAPTER SEVEN

7.0. CONCLUSION
This study has demonstrated that most of the paediatric patients in the study had atypical NS. The predominant lesions were non-MCD with FSGS accounting for 4(44.4%) and immune induced Membranous Nephropathy for 1 out of the 9 patients with biopsy reports. Only two patients during the 7-month period attained remission indicating that even MCD in our patients did not respond favourably to steroid therapy. However, these results cannot be generalised and compared well with larger studies due to the small sample. A larger study needs to be done in order to describe the histological subtypes and clinical characteristics better. This study should also include immunofluorescence studies.

7.1. RECOMMENDATIONS
1. Pre-treatment Renal Biopsy should be performed on all patients with the diagnosis of Nephrotic Syndrome
2. A longitudinal study should be done over a longer period of time in order to describe the lesions seen in patients presenting with NS. This should employ a wider search criterion, i.e. in clinics and other hospitals in Lusaka, for more cases to be identified.
3. There is need to procure more second line drugs for better management of patients with poor response to steroid therapy.
REFERENCES


APPENDIX I

The University of Zambia
Directorate of Research and Graduate Studies

INFORMATION SHEET

A STUDY ON THE CLINICAL CHARACTERISTICS AND HISTOLOGICAL SUBTYPES OF NEPHROTIC SYNDROME IN PAEDIATRIC PATIENTS AT THE UNIVERSITY TEACHING HOSPITAL

1. Why are we giving you this form?
We are giving you this form so as to give you information about the named study and also to give you a chance to ask questions about this study. You can then decide if you would like to take part in this study that is trying to find out the clinical characteristics and what type Nephrotic Syndrome paediatric patients we are see at the University Teaching Hospital (UTH) have. Nephrotic Syndrome is a form of kidney disease where patients will have swelling of the body, protein in urine and increased fat (cholesterol) in the blood. There are several forms or types of nephrotic syndrome and the aim of this study is to find out the types common in children we see at UTH. Each type has different treatment and thus knowing the type helps in choosing the right treatment or the treatment that is likely to work. You have been asked to consider joining this study because you have/your child has nephrotic syndrome.

Who is carrying out this study?
Dr Mashanga Paul is doing the study as partial fulfilment of the requirements for the Master of Medicine in Paediatrics and Child Health at the University Of Zambia, School Of Medicine.
2. Background Information

You are being asked to take part in the above mentioned study, where we would like to find out the common types of Nephrotic Syndrome in children at UTH. This has been necessitated by the increasing number of children who are not responding well to the current treatment because of lack of knowledge of the types of NS. By participating in this study we will be able to get the information that may help to make relevant policies and treatment for this problem in children. We believe this is very vital information to all of us and you would help and benefit by participating in this study.

3. What Happens In This Research Study (Procedure)?

Once you agree to be in the study, you will be asked some and then your child will be examined. Some blood and urine will be collected for tests.

A total of 4 mL only of blood will be collected from cubital fossa or dorsum of the hand with a needle and syringe after cleaning the area with a spirit/alcohol swab. This blood will be subjected to the following tests:

- Serum albumin, serum cholesterol
- Serum creatinine, Urea and Electrolytes
- Liver Function Tests
- FBC
- INR and bleeding time
- Hepatitis BsAg and C serology

10 mL of urine will be collected by asking the participant to submit a urine sample in a small sample bottle and a urine dip stick test done.

Kidney Ultra-sound looking at the location and size of the kidneys will also be done prior to the renal biopsy.

Renal biopsy (the mainstay of the study) will be performed with help of a machine with a computer screen (ultrasound) to visualise the kidney. The participant will be made to lie on a comfortable bed facing down. A pain killer will be administered around the area of the kidney on the back, after thorough cleaning, to ensure that participant is not in pain.
needle will then be introduced around the clean and numb area into the kidney to take a small tissue (size of an office pin) for lab analysis. This analysis will tell us the type of nephrotic syndrome. After this procedure the patient will be observed for 4-6 hours before discharge to ensure that there are no complications.

Note that renal biopsy is an effective and valuable procedure that helps us know the type of nephrotic syndrome, treatment and likely response to treatment. Therefore, knowing the type of nephrotic syndrome will not only help us in making policies but also manage your child better. However, like most medical procedures, a kidney biopsy is not without risk. It may cause pain and bleeding. In this study however, the risk will be minimal based on the careful selection of participants. Furthermore, the procedure will also be performed by experienced doctors.

4. Risks, Inconveniences And Discomforts

Inconveniences include answering questions, typically about 10 to 15 minutes. You will be required to answer the questions as I ask them following the questionnaire. However, if you are uncomfortable to answer certain questions, feel free not to.

The participant may experience some discomfort from the needle prick as blood is being drawn for some tests. To minimize this risk a pain killer called lignocaine spray (an anaesthetic) will be sprayed on the area where blood will be collected.

The participant may also experience discomfort as the kidney biopsy is being done but as explained above, measures will be taken to minimize this. The main risk of this procedure is bleeding. To minimise this risk the clotting profile, which shows how well blood is clotting, will be done prior to the procedure. We will also ensure that all risk factors for bleeding are eliminated during screening. The other inconvenience you will experience is that we may need to observe the participant for at least 6 hours after the procedure before discharge to ensure that any adverse event is attended to promptly.

If you experience any form of stress from answering the questionnaire or during the procedures, you could choose to continue, to discontinue, or to withdraw from the study completely at no penalty to you.
5. **Benefits Of The Research And Benefits To You**

Your participation in the study will be highly beneficial as it will enable us to know the types of nephrotic syndrome and common symptoms and signs in children we see at the University Teaching Hospital. It will also help us know the best treatment alternatives to offer the participant as each type of Nephrotic Syndrome has a unique treatment outcome or response. We will also be able to deduce whether our current treatment strategies are effective or we need to change them.

It will also be of benefit to you as you will be more enlightened on your child’s condition.

6. **Voluntary Participation**

Your participation in the study is completely voluntary and you may choose to stop participating at any time. Your decision not to volunteer will not influence the nature of your relationship with the University Teaching Hospital, now or in the future.

7. **Alternatives To Participation**

If you choose not to participate in this study, you will continue the medical care that you are currently receiving. Choosing not to participate in the study will not affect your relationship with the medical staff or the University Teaching Hospital and therefore you (your child) will continue receiving the treatment being given.

8. **Costs To You**

There will be no costs to you that are directly related to this study.

9. **Payment For Participation**

You will not be paid for your participation in this research.

10. **Confidentiality**

Your name will never be made public by the investigators. The medical record will be treated the same as all medical records at the health centres. A code number that makes it very difficult for anyone to identify you will identify the research information gathered during this study from you. All information will be stored in a secure place. Information from this study maybe used for research purposes and may be published; however, your
name will not be made public by the investigators. It is possible that, after the study is over, we may want to look again at the laboratory and interview record data collected during this study to help us answer another question. If this happens, still your name will not be made public by the investigators.

11. Research Related Injury
In the event that a problem results from a study-related procedure, Dr Mashanga Paul should be notified (0n +260 977 814101) or contact the ERES CONVERGE IRB (see contact details section), and you or your child will be facilitated to seek and receive appropriate medical care at the health facility.

12. Contact Details
Should you want further information about this study or your rights as a participant please use the details provided below.

<table>
<thead>
<tr>
<th>Dr Mashanga Paul</th>
<th>The Chairperson,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principle Investigator,</td>
<td>ERES CONVERGE IRB,</td>
</tr>
<tr>
<td>University Teaching Hospital,</td>
<td>33 Joseph Mwilwa Road,</td>
</tr>
<tr>
<td>Department of Paediatrics and Child Health.</td>
<td>Rhodes Park,</td>
</tr>
<tr>
<td>Lamya: +260 977 814101</td>
<td>LUSAKA.</td>
</tr>
<tr>
<td>Email: <a href="mailto:Pmashanga@gmail.com">Pmashanga@gmail.com</a></td>
<td>Lamya: +260 966765 503</td>
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<tr>
<td></td>
<td>+260 955 155 633</td>
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<tr>
<td></td>
<td>+260 955 155 634</td>
</tr>
<tr>
<td></td>
<td>Email:<a href="mailto:eresconverge@yahoo.co.uk">eresconverge@yahoo.co.uk</a></td>
</tr>
</tbody>
</table>
CONSENT FORM

A STUDY ON THE CLINICAL CHARACTERISTICS AND HISTOLOGICAL SUBTYPES OF NEPHROTIC SYNDROME IN PAEDIATRIC PATIENTS AT THE UNIVERSITY TEACHING HOSPITAL.

Participant
I_____________________________________________________ (participant’s parent or guardian’s name) have been informed about the study. I volunteer to have my child and I participate in the study. I have been informed about the study and I have understood what it involves. I have also been informed that I can withdraw from the study at any point if I feel uncomfortable and that doing so will not affect my relationship with the University Teaching Hospital, now or in future, nor will it affect the treatment my child is currently receiving from the institution. A copy of this form signed by me and one of the study investigators is being given to me.

Signature/Thumb______________________________
Date (dd/mm/yy) _____/_____/_____

Interviewer
I have explained this research study to the participant. I am available to answer any questions now or in the future regarding the study and the participant's rights.

Signature of Investigators & Printed Names
Name _________________________________ Signature ____________________
Date (dd/mm/yy) _____/_____/_____
APPENDIX III

ASSENT INFORMATION SHEET

(For children above 7 years old and above)

A STUDY ON THE CLINICAL CHARACTERISTICS AND HISTOLOGICAL SUBTYPES OF NEPHROTIC SYNDROME IN PAEDIATRIC PATIENTS AT THE UNIVERSITY TEACHING HOSPITAL

Participant
I_____________________________________________________ (participant’s name) have been informed about the study. I volunteer to participate in the study. I have been informed that I can withdraw from the study at any point if I feel uncomfortable and that doing so will not affect my relationship with the University Teaching Hospital, now or in future, nor will it affect the treatment I am currently receiving from the institution. A copy of this form signed by me and one of the study investigators is being given to me.

Signature/Thumb___________________________

Date (dd/mm/yy) ____/____/____

Interviewer
I have explained this research study to the subject. I am available to answer any questions now or in the future regarding the study and the participant's rights.

Signature of Investigators & Printed Names

Name_________________________________ Signature ______________________

Date (dd/mm/yy) ____/____/____
APPENDIX IV

DATA COLLECTION SHEET

A STUDY ON THE CLINICAL CHARACTERISTICS AND HISTOLOGICAL SUBTYPES OF NEPHROTIC SYNDROME IN PAEDIATRIC PATIENTS AT THE UNIVERSITY TEACHING HOSPITAL

Identification code :
Initials of participant :
Participant study number:

Part I: Demographics
a) Age: …….. Years ………. Months
b) Sex: 1) Male 2) Female
c) Race: 1) Asian 2) Arabs 3) blacks 4) Whites

Part II: Presenting Complaints:

III: Review of systems:

a) Cardio-Respiratory system:
   1) Normal 2) Abnormal , specify

b) Gastrointestinal system:
   1) Normal 2) Abnormal , specify

c) Genital-urinary system:
   1) Normal 2) Abnormal , specify

d) Neurology system:
   1) Normal 2) Abnormal , specify

e) Other systems
   1) Normal 2) Abnormal , specify

Part IV: Medical History

- Age at diagnosis of Nephrotic Syndrome
- Past Medical History
1. Diabetes mellitus  
2. Sickle Cell disease  
3. Hepatitis B/C  
4. Severe Malaria requiring ICU admission  
5. HIV  
6. Schistosomiasis  
7. None of the above  

Part V: Drug History  
- Date of starting Steroid therapy:  
- Current Medication  

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<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
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<td>Cyclophosphamide</td>
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</tr>
<tr>
<td>Levamisole</td>
<td></td>
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</tbody>
</table>

- Others Medications  
- If HIV positive and on HAART,  
  - Type of HAART  
  - Duration on HAART  

- Number relapses in the last 1 year:  

Part VI: PHYSICAL EXAMINATION  
a) General appearance: 1) Well 2) Ill  
b) Vitals  
Pulse:  
Respiratory rate:  
Temp:  
c) Anthropometry  
Weight:  
Height:  
Weight for height standard deviation:  
BP:  
d) General examination
Pallor: 1) No pallor 2) mild 3) moderate 4) severe

Oedema: 1) yes 2) no

e) systems/organs

<table>
<thead>
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<th>System/organ</th>
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<th>Specify findings</th>
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</tr>
<tr>
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</tr>
<tr>
<td>Ears, Nose</td>
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**TESTS DONE ON PARTICIPANT**

<table>
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<td>Kidney Biopsy</td>
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Name of doctor: ………………………………. Signature: ……………………….

Data Entry Date: ……./……./……….

Data Entry Number: 

39