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Early Detection of Renal Injury in Children with Sickle Cell Anaemia using Microalbuminuria in a Tertiary Health Institution in Southern Nigeria

Détection précoce des lésions rénales chez les enfants atteints d'anémie falciforme grâce à la microalbuminurie dans un établissement de santé tertiaire du sud du Nigeria

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ABSTRACT

BACKGROUND: Sickle cell anaemia (SCA), one of the causes of morbidity and mortality in children is associated with a large spectrum of systemic complications including sickle cell nephropathy (SCN). Microalbuminuria has been used as a marker of preclinical glomerular damage in these patients. This study aimed at detecting early, renal injury in children with SCA aged 1–17 years, highlighting associations and predictors of microalbuminuria in these children.

METHODS: 102 known HbSS children aged 1–17 years in steady state were recruited into a cross-sectional study. Socio-demographic and clinical findings were recorded. Albuminuria was assayed with spot urine using a quantitative method. Urine creatinine concentration was estimated using the Roche reflotron test strips for quantitative determination of creatinine in blood, serum, plasma and urine. Albumin to creatinine ratio (ACR) was then calculated. Microalbuminuria was defined as ACR of 30–300mg/g.

RESULTS: Microalbuminuria was detected in 22.5% of SCA patients in our cohort. Age ($p=0.001$), gender ($p=0.000$), packed cell volume ($p=0.047$) showed a significant relationship with the occurrence of microalbuminuria in this study. Increasing age (OR=1.72, CI=1.22–2.44, $p=0.002$), female gender (OR=0.09, CI=0.01–0.95, $p=0.04$) and lower packed cell volume (OR=0.49, CI=0.26–0.90, $p=0.02$) emerged as independent risk factors associated with the occurrence of microalbuminuria in the study population.

CONCLUSION: Renal injury occurs in a high proportion of patients with SCA. Routine screening of all patients with SCA as part of their follow up is therefore recommended to identify patients with early renal injury for proper management. WAJM 2020; 37(4): 412–417.

Keywords: Microalbuminuria; Preclinical Glomerular Renal Injury; Sickle Cell Anaemia.

RÉSUMÉ

Contexte : La drépanocytose, l'une des causes de morbidité et de mortalité chez les enfants, est associée à un large éventail de complications systémiques, dont la drépanocytose (NCS). La microalbuminurie a été utilisée comme marqueur des lésions glomérulaires précliniques chez ces patients.

Cette étude visait à détecter précocement les lésions rénales chez les enfants atteints de néphropathie à cellules falciformes âgés de 1 à 17 ans, en mettant en évidence les associations et les prédicteurs de la microalbuminurie chez ces enfants.

Méthodes : 102 enfants atteints d'ACS connus, âgés de 1 à 17 ans et en état d'équilibre, ont été recrutés pour une étude transversale. Les résultats socio-démographiques et cliniques ont été enregistrés. L'albuminurie a été dosée par une méthode quantitative à l'aide d'urine ponctuelle. La concentration de créatinine dans l'urine a été estimée à l'aide des bandelettes réactives au reflotron de Roche pour la détermination quantitative de la créatinine dans le sang, le sérum, le plasma et l'urine. Le rapport entre l'albumine et la créatinine (ACR) a ensuite été calculé. La microalbuminurie a été définie comme un ACR de 30–300mg/g.

Résultats : La microalbuminurie a été détectée chez 22,5 % des patients atteints de SCA dans notre cohorte. L'âge ($p=0,001$), le sexe ($p=0,000$), le volume de cellules emballées ($p=0,047$) ont montré une relation significative avec l'apparition de la microalbuminurie dans cette étude. L'âge croissant (OR=1,72, CI=1,22–2,44, $p=0,002$). Le sexe féminin (OR=0,09, CI=0,01–0,95, $p=0,04$) et un volume de globules rouges plus faible (OR=0,49, CI=0,26–0,90, $p=0,02$) sont apparus comme des facteurs de risque indépendants associés à l'apparition de la microalbuminurie dans la population étudiée.

Conclusion : Les lésions rénales surviennent chez une forte proportion de patients atteints d'ACS. Il est donc recommandé de procéder à un dépistage systématique de tous les patients atteints de SCA dans le cadre de leur suivi afin d'identifier les patients présentant une lésion rénale précoce pour une prise en charge adéquate.

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Mots clés: Microalbuminurie; Glomérulaire préclinique lésion rénale. L'anémie falciforme.

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Abbreviations: ACEI, Angiotensin Converting Enzyme Inhibitors, **ACR**, Albumin Creatinine Ratio, **BMI**, Body Mass Index, **IHREC**, Institutional Health Research and Ethical Committee, **PCV**, Packed Cell Volume, **SCA**, Sickle Cell Anaemia, **SCN**, Sickle Cell Nephropathy, **SPSS**, Statistical Package for Social Sciences

INTRODUCTION

Sickle cell anaemia (SCA) remains one of the causes of morbidity and mortality in children globally.¹ It accounts for 5% of under-five mortality in the African continent with more than 9% occurring in West Africa and up to 16% in individual West African countries.² In Nigeria up to 26.5% of deaths in children aged 5 to 15 years is due to SCA.³ It is an autosomal recessive disorder that is due to the substitution of the amino acid valine for glutamic acid at the sixth position of the beta chain.⁴ Sickle cell anaemia is associated with systemic complications such as sickle cell nephropathy.⁵

Sickle cell nephropathy comprises of all the functional and structural abnormalities of the kidneys seen in sickle cell disease.⁵ The kidneys are particularly susceptible to sickling in SCA. This is because of the absence of collateral circulation and the presence of sickling promoting factors of the renal medulla such as hypoxia, acidosis and hypertonicity.⁶ This sickling leads to vaso-occlusion, ischemic injury and loss of renal mass.⁶ The renal complications of SCN include haematuria, proteinuria, tubular disturbances and chronic kidney disease. Thus glomerular filtration, blood pressure regulation, tubular function and electrolyte metabolism are all disturbed.⁷ Due to increasing life expectancy of sickle cell anaemia patients, the prevalence of end stage kidney disease (ESRD) has significantly increased in the last few decades becoming an independent factor for mortality in these patients.⁸ Plat *et al*⁹ in analysing the life expectancy and risk factors for early death in sickle cell disease ascribed 18% of the deaths to chronic end organ involvement predominantly renal in the form of SCN.

Microalbuminuria in SCA is mainly due to hyperfiltration-hyperperfusion injury leading to glomerular damage.⁶ It precedes proteinuria that may progress to chronic kidney disease in SCN.¹⁰ However this progression can be retarded by the use of Angiotensin Converting Enzyme Inhibitors (ACEI). Even with this benefit, the use of microalbuminuria in evaluation of SCA patients has not received sufficient attention particularly in Nigeria.¹¹ In addition there is still a

paucity of information about SCN in sub-Saharan Africa which has the highest burden of SCA.¹⁰

METHODS

This cross-sectional study was conducted between November 2016 and March 2017 at the Paediatric Haematology clinic of University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria. The study population was made up of 102 children aged 1–17 years with sickle cell anaemia in steady state. Steady state was defined as apparently well without fever, blood transfusion or crises in the preceding four weeks.¹² Approval for the study was obtained from University of Uyo Teaching Hospital's Institutional Health Research and Ethical Committee (IHREC). A written informed consent was obtained from parent/guardians of all the children included in the study after they were properly informed of the nature of the study and the study objective. Strict confidentiality was emphasized. Assent was obtained from children older than 7 years.

The sample size was determined using the formula: $n = Z^2pq/d^2$, where n =minimum required sample size, Z =the standard score, corresponding to a given confidence interval, in this case 1.96 for 95%, p =the best estimate of population prevalence rate, $q=1-p$, d = precision of result desired. The average of prevalence rates from other Nigerian studies gave prevalence rate of 16.7%.¹¹⁻¹³

HbSS children who had fever, crises or blood transfusion in the preceding four weeks were excluded from the study. Also excluded were HbSS children who had confirmed nephrotic syndrome, systemic disease such as diabetes mellitus or those on renal replacement therapy.

A proforma designed specifically for the study was used to obtain all relevant history and clinical data from subjects recruited for the study. Each child was assigned a socio-economic index using the method by Oyedeji.¹⁴

General clinical examination was carried out checking for pallor, peripheral oedema and organomegaly. Weight was measured using a digital scale or basinet scale as appropriate for the subject's age to the nearest 0.1kg. Height was measured using a wall-mounted stadi-

ometer to the nearest 0.5cm. The recumbent length was taken for children less than 24 month using an infantometer. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meter.¹⁵ Axillary temperature was recorded in degrees Celsius (°C) using a mercury in glass thermometer. A child was regarded as febrile if temperature was greater than 37.5°C.¹⁶

Sample Collection

Parents/guardians of recruited subjects and the subjects were instructed on how to collect mid-stream urine. 10mls of fresh urine was collected into a universal bottle without addition of preservatives. This was divided into two plain sample bottles for urine albumin and urine creatinine estimation. Samples for urine albumin was sent to the laboratory, frozen at -20°C for samples to be batched for analysis. About 3mls of blood was obtained and put into an EDTA bottle for, packed cell volume (PCV) measurement using the microhaematocrit technique.¹⁷

Urine creatinine was estimated using test strips for quantitative determination of creatinine in blood, serum or urine according to the manufacturer's instruction. [REF 1 0886874. Roche Diagnostics Ltd BN7 1LG UK]. This was done within one hour of collection using the point of care Roche Reflotron plus machine.

Urine albumin was determined using MICROALBUMIN™, an immunoturbidimetric assay for quantitative determination of microalbuminuria, [LTA Sr I, Via Milano Italy CAT NO: UK00510. LOT: B 210:16], with an analytical sensitivity cut-off of 3mg/dl.

Urine albumin to creatinine ratio was mathematically derived. The presence of microalbuminuria was defined as albumin/creatinine ratio (ACR) of 30–300mg/g creatinine.¹⁸

Data Analysis

The data generated from the study was entered into Microsoft Excel spreadsheet from the completed proforma. This was analysed using the statistical package for social sciences (SPSS) version 23. Results were presented with the use of frequency tables and pie

charts. The number of participants with albumin/creatinine ratios (ACR) of between 30–300mg/g creatinine were adjudged to have microalbuminuria. Chi-square test was done to assess the relationship between sociodemographic variables. Independent t-test analysis was done to ascertain the differences between the variables. All analysis was done at 5% level of significance and p-value of less than 0.05 at 95% confidence interval was considered statistically significant. Univariable and multivariable logistic regression models were used to identify independent associations with the development of microalbuminuria in the study population. Variables with p-value of the wald statistic <0.25 at the univariate level were included in the final multivariate model. P-value of <0.05 at the multivariable level or 95% confidence interval not inclusive of 1 were regarded as having independent association with the occurrence of microalbuminuria.

RESULTS

One hundred and five subjects (105) were recruited for this study. Three (3) children were excluded because of fever, (axillary temperature more than 37.5°C) leaving one hundred and two (102) subjects. Table 1 shows the socio-demographic characteristics of the study population. Males were 55.9% and

Table 1: Social Demographic Characteristics of the Study Population

Variable	Frequency (n)	Percentage (%)
Age (years)		
1–5	44	43.2
6–10	34	33.3
11–15	16	15.7
>16	8	7.8
Total	102	100
Gender		
Male	57	55.9
Female	45	44.1
Total	102	100
Socio-economic class		
1	17	16.6
2	62	60.8
3	12	11.8
4	11	10.8
5	0	0
Total	102	100

Table 2: Values of ACR, Urine Creatinine and Urine Albumin in the Study Population

Variable	With MA	Without MA
ACR(mg/g)	53.18±21.67	15.49±9.02
Urine Creatinine (mg/dl)	51.47±25.00	40.40±17.73
Urine Albumin (g/l)	2.59±1.25	0.69±0.54

Table 3: Prevalence of Microalbuminuria in different Age Groups of Children with Sickle Cell Anaemia

Age (years)	With MA (%)	Without MA (%)	Total (%)	χ ²	P-value
1–5	3 (6.8)	41 (93.2)	44 (100)	7.205	<0.007*
6–10	5 (14.7)	29 (85.3)	34 (100)		
11–15	10 (62.5)	6 (37.5)	16 (100)		
>16	5 (62.5)	3 (37.5)	8 (100)		
Total	23 (22.5)	79 (77.5)	102 (100)		

P<0.05, *Statistically Significant; χ², Pearson Chi Square; MA, Microalbuminuria

Table 4: Clinical Parameters in Children with Sickle Cell Anaemia with and without Microalbuminuria

Micro-albuminuria	Age (Years)	Weight (kg)	BMI (kg/m ²)	Systolic BP (mmHg)	Diastolic BP (mmHg)	PCV (%)
WithMA (N=23)	12.13±4.01	28.04±10.29	22.30±9.95	98.48±11.91	68.70±7.57	22.30±2.62
WithoutMA (N=79)	6.89±3.81	23.94±8.59	20.83±7.70	95.70±11.68	66.46±7.03	23.84±3.39
t-value	5.745	1.924	0.066	1.001	1.312	-2.014
p-value	<0.001*	0.057	0.947	0.319	0.189	0.047*

P<0.05, *Statistically Significant; df, Degree of freedom (100); BMI, Body mass index; N, Number of subject.

Table 5: Logistic Regression Model showing Independent Association with Occurrence of Microalbuminuria in Children with Sickle Cell Anaemia.

Parameter	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age (years)	1.52(1.27–1.82)	0.001	1.72 (1.22–2.44)	0.002
Gender (male)	0.29(0.09–0.86)	0.03	0.09(0.01–0.95)	0.04
PCV	0.70(0.56–0.87)	0.002	0.49(0.26–0.90)	0.02

females were 44.1% of the study population with a male to female ratio of 1.2:1. The mean age of the subjects was 8.07 ± 4.42 (range 1–17years). Majority of the subjects (77.4%) belonged to social class 1 and 2. Social class 2 had the greatest percentage (60.8%). No subject belonged to social class 5 (Table 1).

Microalbuminuria was detected in 22.5% of the subjects in this study. (95% C.I 13.2–31.7%). ACR in the study population ranged from 3–105mg/g with a mean ACR of 53.18 ± 21.67 in those with microalbuminuria and 15.49 ± 9.02mg/g in those without microalbuminuria (Table 2).

Fifteen (65.2%) of the subjects with microalbuminuria were older than 10 years, while the lowest proportion of subjects 3 (13.0%) with microalbuminuria was found in age group 1–5 years. Considering the prevalence rates in different age groups, the prevalence of microalbuminuria was higher in the age groups 11–15 years (62.5%) and >16 years (62.5%). There appears to be an increasing prevalence of microalbuminuria as the age of the subjects increased (Table 3).

The proportion of the subjects with microalbuminuria was significantly higher in the female than in the male subjects ($p=0.000$). However, the prevalence of microalbuminuria was not affected by the socio-economic class of the subjects in the study ($p=0.246$).

The mean value of PCV (22.30 ± 2.62) in subjects with microalbuminuria was significantly low when compared with subjects without microalbuminuria ($p=0.047$). There was no significant difference in the blood pressure, weight, body mass index among the group of subjects with and without microalbuminuria (Table 5).

A logistic regression model was developed to adjust the age, gender and PCV. Age, ($p=0.001$) gender, ($p=0.04$) and PCV ($p=0.02$) were independently associated with the occurrence of microalbuminuria. For every year increase in age, the odds ratio of microalbuminuria was 1.72 (95% C.I 1.22–2.44) after adjusting for the effect of gender and PCV. For each 1% increase in PCV, the likelihood of having microalbuminuria reduced by 51%. For gender, the males had an odds ratio of 0.09 compared to the females (reference group) after adjusting for age and PCV (Table 5).

DISCUSSION

Microalbuminuria detected in 22.5% of steady state HbSS patients in this study compares favourably to the reports of 19.4%¹⁹ in the USA, 18.4%¹¹ in Jamaica and 24%²⁰ in Tanzania. All these studies used the quantitative method, considering ACR like the present study with the same cut-off values of 30mg/g. The prevalence in this study is also similar to reported prevalence rates of 18.5%¹² and 20.3%¹³ in some Nigerian studies using micral strips, a semi-

quantitative method of microalbumin estimation. The similarity in these prevalence rates in the Nigerian studies may suggest that the use of micral strips, though less sensitive but cheaper is a useful screening tool for microalbuminuria in children with sickle cell anaemia.

In contrast, the prevalence rate of 22.5% in this study was much higher than 11.3% reported by Solarin *et al*¹¹ in South-West Nigeria who used the same quantitative methodology. This difference in the same country could be due to difference in the ages of the study population. The present study considered children aged 1–17 years of age unlike Solarin *et al*¹¹ whose study population consisted of children aged 5–15 years of age. This study noted the occurrence of microalbuminuria in children less than 5 years of age and children more than 16 years of age which were not part of the study by Solarin *et al*.¹¹ Various factors may modify the differences in presentations of these patients. These factors include, the levels of foetal haemoglobin, presence of alpha gene deletion, beta gene cluster haplotype, genetic and environmental factors.⁴ These may have played a role in the high prevalence of microalbuminuria noted in this study. Children that do not receive optimal care in the form of good nutrition, routine drugs and adequate hydration are at risk of having frequent crises which may lead to more complications of sickle cell anaemia including SCN.

The occurrence of microalbuminuria in this study increased with increasing age. This finding is comparable with reports from other studies.^{18,20} Aloni *et al* reported the proportion of microalbuminuria in sickle cell anaemia children more than 9 years to be 66.7% with the mean age for the occurrence of microalbuminuria to be 10.5 ± 4.2 years.¹⁰ Studies in Nigeria also reported similar findings.^{11–13} Sickle cell nephropathy is a progressive condition that begins in childhood. Older patients may have experienced a greater number of ischaemic crises leading to infarction of both medullary and cortical vessels with variable loss of renal function.^{11,21}

However, microalbuminuria was reported in three subjects less than 5

years of age in this study, the youngest being 3 years and 5 months old. This finding was also noted by Alvarez *et al*²² in USA, King *et al*⁸ in Jamaica, Eke, *et al*¹² and Solarin *et al*¹¹ in Nigeria but contrasts with Dharnidharka *et al*¹⁸ who reported that microalbuminuria did not occur before 7 years of age. The three subjects in this study were all diagnosed to have HbSS in infancy, had more than two hospital admissions for crises since diagnosis and had received blood transfusions at least once since diagnosis. These factors depicted severity of disease in these children. Finding microalbuminuria in this age group further strengthens the need for early screening and adequate follow up of these patients as the pathophysiological process starts in early childhood.

Female gender as an independent factor associated with the occurrence of microalbuminuria in this study has also been documented in some other Nigerian studies^{11–13} although their relationship was not statistically significant. Ranque *et al*²³ in a multinational study reported female gender as a predictor of microalbuminuria. The reason for this finding has not been clearly understood, however, genetic factors and the risk of urinary tract infection in females have been proposed as possible reasons by various authors.^{12,13,18} Patients with SCD have an amplified vulnerability to urinary tract infection because of abnormally dilute and alkaline urine which favours bacterial proliferation.²⁴ The female gender preference has been linked to the structurally shorter urethra and the relative deficiency of secretory IgA antibody response from the mucosal surface in the urinary tract of females compared to males.²⁵ These speculations cannot be authenticated in this study as subjects with symptoms of urinary tract infection were excluded.

Packed cell volume being one of the independent variables associated with occurrence of microalbuminuria in this study is similar to what has been reported in other studies.^{11–13,19} In contrast to this finding, Shatat *et al*²⁶ considering haemoglobin concentration reported no relationship with the occurrence of microalbuminuria. This could have been because it was a retrospective study with

the disadvantages of poor data quality and differential loss to follow up. They relied on codes to identify patients with SCD from the emergency room. This could have resulted in some missed data as there is a possibility of errors related to coding. Albuminuria likely results from glomerular hyperfiltration together with endothelial injuries from chronic haemolysis, tissue hypoxia and metabolites formation.²³ Chronic haemolysis can lead to low PCV and free haemoglobin which can catalyse the formation of free radicals that further damage endothelial cells and trigger vascular inflammation.²³ It is therefore possible that a higher steady state packed cell volume could be protective of sickle cell nephropathy.¹¹ A longitudinal study with chronic blood transfusion programme will be needed to confirm its potential reno-protective effect.

The highest prevalence of microalbuminuria noted in subjects in social class II, could be explained by the fact that social class II had the largest number of subjects. University of Uyo Teaching Hospital (UUTH) is in the state capital, an urban area where the elites reside. It has been documented that 70–90 % of medical financing in Nigeria is “out of pocket” spending.²⁷ It maybe therefore inferred that only those with financial capacity, a reflection of their social class present to UUTH for management. It is also possible that HbSS patients of other social classes present to secondary health care centres for treatment and follow up. However, considering the number of subjects in social class IV, it also had a high prevalence of subjects with microalbuminuria. A contribution of factors such as poverty, poor health seeking behaviour and level of care given by the caregivers to these patients could be considered as possible causes. These factors could predispose the patients to more frequent crises, leading to systemic complications such as SCN. Microalbuminuria occurring more in patients with low socioeconomic class was a similar finding in some studies done in Nigeria.^{12,13} Studies done outside Nigeria did not consider socioeconomic class as an association to the occurrence of microalbuminuria in SCA children.

The subjects with microalbuminuria

weighed more and had higher BMI than those without microalbuminuria in this study. This was also reported by Solarin *et al*¹¹ in Nigeria but was in contrast to the report by King *et al*⁸ in Jamaica. This may be because most of the subjects with microalbuminuria belonged to the upper social class and thus may have received better care and nutrition. It has also been reported that poor socioeconomic class reflects adversely on the nutritional status of children with SCA.²⁸ Hence, it is possible to infer that children in the higher social class are fed more nutrient rich diets which reflects in their anthropometry.

A higher mean systolic and diastolic blood pressure in children with microalbuminuria in this study is similar to what was reported in Benin, Nigeria and in Democratic Republic of Congo.^{10,13} It has been suggested that relative systemic hypertension in sickle cell patients is associated with the risk of chronic kidney disease, thus attempting to explain the possible relationship between systemic blood pressure and microalbuminuria.⁽²⁹⁾ Furthermore, Bartolucci *et al*³⁰ have shown that the baseline to follow up decline in albumin/creatinine ratio is strongly associated with decrease in systolic blood pressure. In addition, decrease albuminuria under hydroxyurea therapy is associated with a reduction of systolic blood pressure between baseline and follow up levels.³⁰

This study being a hospital-based study does not reflect the true community picture. In addition, the use of spot urine sample is a limiting factor due to the inability to exclude the effect of orthostatic proteinuria. Screening microalbuminuria in three serially collected urine samples over a three-month period with two positive results would have provided a better result for persistent microalbuminuria. A longitudinal study that will follow up these patients into adulthood to ascertain the persistence and/or progression of microalbuminuria is needed. The quantitative methodology done however gives room for follow up into adulthood of these patients and the possibility of analytical studies in future.

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