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Renal abnormalities among children with sickle cell anaemia

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Abstract*: Introduction:* Sickle cell anaemia (SCA) is a non-communicable disease of public health significance. SCA is characterized by chronic red blood cell haemolysis and vaso-occlusion which further complicated by nitric oxide deficiency, causes oxidative damage to the body organs especially the kidneys.
Objectives: To document the prevalence of renal function and structural abnormalities in children with SCA in a teaching hospital in north western Nigeria.
Materials and Methods: One hundred and ten subjects with SCA in steady state without known renal or cardiac abnormalities were enrolled and matched for age and sex with controls (haemoglobin AA). Interviewer-administered questionnaires, clinical examination and renal ultrasound scans were carried out. Urinalysis, spot urine albumin creatinine ratio and serum creatinine were carried out using standardized laboratory methods.
Results: Eleven (10.3%) children with SCA had haematuria while 6.5% had overt proteinuria. Children with SCA who had proteinuria were five times more likely, to develop haematuria than the controls with proteinuria ($p = 0.03$). Microalbuminuria was found in 24.3% of children with SCA. The mean estimated glomerular filtration rate was normal for both subjects and controls. Only three (2.8%) of the SCA subjects had increased renal echogenicity all of whom had microalbuminuria and were older than nine years.
Conclusion and recommendations: Renal abnormalities were found in children with SCA occurring as early as 4 years of age. Regular screening for renal disease in children with SCA is recommended to ensure management modalities are instituted early.

Key words: SCA, Renal abnormalities, haematuria, proteinuria, renal size, estimated glomerular filtration rate

Introduction

Sickle cell nephropathy encompasses the structural and functional abnormalities of the kidney seen in patients with sickle cell haemoglobinopathy (an autosomal recessive genetic disorder[1,2]) in the absence of other secondary causes of kidney disease.[3] Up to 1 in 5 people with SCD develop renal abnormalities which may progress to chronic kidney disease (CKD).[4]The haemodynamic changes of chronic anaemia and the consequences of vaso-occlusion which are especially marked within the renal medulla in SCA results in abnormalities in renal structure and function [5]that begin in childhood. Functional abnormalities include impaired urinary concentration, causing hyposthenuria,[6] enuresis, proteinuria, nephrotic syndrome, haematuria, hypertension, acute kidney injury, chronic kidney disease and end-stage renal disease.[7] Chronic kidney disease is an emerging non communicable disease of public health significance world wide. Progression of CKD to end stage renal disease (ESRD) may be delayed or halted using various modalities like lifestyle and dietary modifications and use of drugs like hydroxyurea and angiotensin converting enzyme inhibitors (ACEI) and receptor blockers (ARB).[2] Over the years, there have been advances in the management of SCA, changes in lifestyle, diet, wide spread use of non-steroidal anti-inflammatory drugs (NSAID's), herbs and substandard drugs all of which may affect the kidney.[8] The aforementioned, coupled with the increase in CKD noted worldwide prompted this study to detect abnormalities in renal structure and function in children with SCA in the locality.

This study therefore aimed to determine renal function and ultrasonographic findings in children with sickle cell anaemia in a tertiary hospital north western Nigeria.

Materials and Methodology

A cross sectional study was carried out in the paediatric haematology and oncology clinic between August 2014 to January 2015 following approval from the Human Research and Ethics Committee

One hundred and ten subjects with SCA in steady state without any prior known renal or cardiac abnormalities were consecutively sampled, enrolled and matched for age and sex with controls (haemoglobin AA). A structured interviewer-administered questionnaire was administered and clinical examination carried out. Renal glomerular function was assessed using urinalysis, micro-albuminuria a sensitive marker of renal disease and estimated glomerular filtration rate (eGFR). Renal structure was assessed using renal ultrasound scans.

The first consecutive 10 children who met the inclusion criteria were enrolled for the study each clinic day. Subjects were children with haemoglobin electrophoretic diagnosis of SCA (Hb SS and Hb SS+F) aged two to 18 years old who were in their steady state. Steady state was defined as a child with SCA who has remained symptom-free for the three weeks preceding enrolment into the study. Excluded from the study were subjects with known cardiac disease (congenital or acquired) or hypertension and those with urinary tract infection (UTI) or symptoms suggestive of UTI. Urinary tract infection was considered present for this study in subjects with positive leucocyte esterase and/or nitrite on urinalysis and/or un-centrifuged urine microscopy of ≥1 leucocytes per high power field. Also excluded where children with known congenital structural renal conditions (posterior urethral valves, renal artery stenosis and children who had been on antibiotics treatment in the last two weeks preceding the study.

A spot sample of 10 ml of urine was collected by clean catch method in a universal specimen bottle for urinalysis at the clinic; Urine was tested immediately with Combi 11® dipstix. Only children with samples that tested negative to nitrites and leucocyte esterase were recruited. In those with proteinuria (≥+ 1 protein on dipsticks) or haematuria (≥+1 blood on dipsticks), urine microscopy was carried out to rule out UTI. All samples that tested negative for proteinuria, nitrite and leucocyte esterase by dipstix and normal urine microscopy was stored at -20^{o}C for quantification of micro-albuminuria using a semi-quantitative immunoturbidimetric assay.
Venous blood (2.5ml) was collected via a venepuncture using a peripheral vein following swabbing of the skin with 70% alcohol and povidone iodine and assayed for creatinine. Serum creatinine was assayed using the Selectra XL® automated chemistry analyser (ELITech group, vital scientific Chicago, IL (USA)) which is based on the Jaffe's reaction. Each assay was validated using commercial quality control samples, standards and previously assayed human sera. Laboratory reference values for serum creatinine were used and the eGFR was calculated from the serum creatinine using the original Schwartz formula. Micro-albuminuria was assayed using Turbilatex® a quantitative turbidimetric kit manufactured by Labkit diagnostics limited. Microalbuminuria was considered as an albumin creatinine ration (ACR) of 30-300mg/g.

Abdominal ultrasound scan was carried out using the Mindray® pro sound model ultrasonography machine with Doppler facilities using a convex (curved array) transducer at 3.75MHz. The kidneys were evaluated in the supine and prone positions. The longitudinal lengths of the kidneys were measured and compared with paediatric normograms. The ultrasonographic appearance was described based on consensus between two ultrasonographers (qualified radiologists) noting the presence of increased parenchymal echogenicity, calyceal clubbing, renal scarring and other abnormalities. An increase in reflectivity throughout the kidney and poor/loss corticomedullary differentiation was defined as diffusely increased renal echogenicity.

Results

Of the 110 subjects enrolled, five of the subjects did not report back following initial screening showing proteinuria despite efforts to get across to them (two control and three subjects with sickle cell anaemia). Two urine samples for the controls were lost in the laboratory due to spillage. A final population consisting of 107 subjects with haemoglobin SS and 106 controls with haemoglobin phenotype AA following haemoglobin electrophoresis was used. The female: male ratio was 1:1.03. The ages ranged from 2 to 17 years for the SCA subjects, and 2.2 to 18 years for the controls. The mean age for the SCA group was 8.9 ± 4.0 years while that for the control was 8.2 ± 3.8 years (p = 0.16).

Thirty-three (30.8%) of the children with SCA had proteinuria. These included 26 (24.3%) who had microalbuminuria while the rest had overt proteinuria (≥1+). The prevalence of proteinuria was significantly more (χ^2 = 6.59, p = 0.01) than that in the control group who had an overall prevalence of proteinuria of 16 (15.1%).
Microalbuminuria was significantly more in subjects (24.3%) than controls (p = 0.04). Table 1. Sickle cell anaemia subjects were 2.1 times more likely to have microalbuminuria than controls. There were 17 (31.5%) female subjects with SCA who had microalbuminuria, they were not significantly more than the 9 (17.0%) male subjects with SCA who had microalbuminuria (χ^2 = 2.3, p = 0.1). Microalbuminuria apparently increased with age but this was not statistically significant with χ^2 for linear trend = 0.6, p = 0.4. Other biometric and laboratory parameters were not found to significantly affect the occurrence of proteinuria in children with SCA in this study.

The overall mean estimated glomerular filtration rate (eGFR) for subjects with SCA was not significantly higher (101.4 ± 27.6 ml/min/1.73 m^2) than that in the controls (98.9 ± 26.4 ml/min/1.73 m^2; t-test = 0.68, p =

0.5). The mean eGFR, increased with age for the females and males in both the SCA and control groups. There was also no significant difference in the mean eGFR of subjects and controls with proteinuria and those without proteinuria. Table 2

Table 1: Prevalence of microalbuminuria in sickle cell anaemia and control subjects

Parameter	SCA n (%)	Control n (%)	Total n (%)
Microalbuminuria	26 (24.3)	14 (13.2)	40 (18.8)
No microalbuminuria	81 (75.7)	92 (86.8)	164 (81.2)
Total	107 (100.0)	106 (100.0)	213 (100.0)

$\chi 2 = 4.3$, df = 1, p= 0.04, OR = 2.1, 95% C.I 1.0 - 4.3

Table2: Mean estimated glomerular filtration rates (eGFR) of sickle cell anaemia and control subjects by age group and gender

		Mean eGFR ± SD (ml/ min/1.73 m2)			
Gender	Age (years)	SCA	Control	t-test	p-value
Female	0-4	77.9 ± 13.7	76.3 ± 20.8	0.19	0.8
	5-9	90.4 ± 20.4	88.3 ± 16.7	0.37	0.7
	10-14	108.4 ± 39.8	107.9 ± 23.1	0.06	0.9
	15-19	127.2 ± 15.1	111.9 ± 9.8	1.94	0.09
Male	0-4	80.1 ± 13.9	80.4 ± 29.2	0.03	0.9
	5-9	94.2 ± 20.8	89.8 ± 31.3	0.5	0.6
	10-14	109.6 ± 20.3	108.4 ± 20.6	0.12	0.9
	15-19	136.9 ± 18.8	133.9 ± 23.1	0.17	0.8

SCA = sickle cell anaemia, eGFR= estimated glomerular filtration

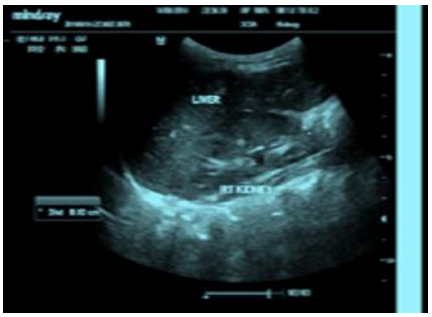
The mean kidney lengths and widths were significantly higher in the SCA groups compared with the controls. Table 3. While the mean lengths and widths for the left kidney were more than the right kidney in both SCA and controls groups, the differences were not found to be significant (p >0.05). Three (2.8%) of the subjects with SCA (two females and one male) had diffuse increased renal echogenicity, a non-specific indication of renal parenchymal disease. All of the subjects with SCA with increased renal echogenicity were between 9 and 14 years had microalbuminuria though none had proteinuria or haematuria demonstrable on urine dipstix, raised blood pressure or abnormal estimated glomerular filtration rates.

Table 3: Mean renal lengths and widths in sickle cell anaemia and controls

Mean kidney measurement mm (SD)	SCA n = 107	Control n= 106	t-test	p value
Right length	86.2 (13.0)	79.9 (11.1)	-3.76	<0.0001*
Left length	87.1 (13.1)	80.2 (10.9)	-4.1	<0.0001*
Right width	36.7 (4.9)	34.0 (3.5)	-4.64	<0.0001*
Left width	37.1 (5.0)	34.1 (3.9)	-4.86	<0.0001*

SCA = sickle cell anaemia, SD- standard deviation, *statistically significant

Fig 1: Ultrasound image of the right kidney showing increased renal echogenicity in a nine-year old girl with sickle cell anaemia



Discussion

The prevalence of proteinuria among sickle cell anaemia subjects was 30.8% most of which was from microalbuminuria and was significantly more than in the controls. This study recorded a prevalence of overt proteinuria using dipstix of 6.5% among children with sickle cell anaemia, this was similar to finding by Ugwu *et al*[9] in Port Harcourt, Anigilage and Adedoyin[10] in Ilorin, and Wigfall *et al*[11] in the USA, who found a prevalence of 7%, 6.7% and 6.2% respectively. However, while the finding of overt proteinuria among SCA subjects by Ugwu *et al* and Wigfall *et al* were significantly higher in subjects with SCA compared to controls, this was not found to be so in this study. The lack of significant difference in the occurrence of overt proteinuria in subjects with SCA when compared with controls may be as a result of the controls being drawn from the hospital setting and some may have had undocumented risk factors for proteinuria.

Microalbuminuria was significantly more in subjects with SCA compared with controls. SCA subjects were found to be 2.5 times as likely to have microalbuminuria when compared to controls. This is similar to 26.5% of SCA subjects with microalbuminuria recorded by Dharnidharka*et al*[12] in a study in the United States of America (USA) among 102 SCA subjects. These findings are however, higher than that recorded by Imuetinyan *et al*[13]in Benin and Eke *et al*[14] at Enugu where 20.3% and 18.5% respectively of their SCA subjects had microalbuminuria. In the studies by Dharnindakar,[12] Imuetinyan[13] and Eke,[14]microalbuminuria was significantly higher in children with SCA than controls. The higher prevalence of micro-albuminuria in this study and Dharnindakar *et al*[12] compared to the Benin and Enugu findings may be due to the difference in the method of assay employed. Micral strips which are semi -quantitative methods were used in Benin[13]and Enugu[14],whereas a quantitative method was used in this study and in the study by Dharnidharka*et al*[12]. Prevalence of microalbuminuria from the study by Solarin *et al*[15] in Lagos using both semi quantitative micral strips

(38.8%) and quantitative methods (11.3%) varied. This disparity is thought to be due to methodology.[15] The female preponderance of subjects with microalbuminuria in this study was also documented by Imuetinyan[13], Solarin[15]and Dharnidhakar *et al*.[12] Microalbuminuria was found in children less than five years in this study, similar to the study done by Imuetinyan *et al*[13] in Benin but in contrast with findings by Gusach *et al*[16] who documented that microalbuminuria was noted in those 10 years or older and Dharnidharka *et al*[12]in the USA who documented no microalbuminuria under the age of seven years. The later occurrence of microalbuminuria may be as a result of possible effect of diagnosis of SCA at birth through routine screening in developed countries like the USA and England where screening for sickle cell disease has been recommended for all infants, regardless of ethnic origin.[17]It was found in this study that there was a slight increase in prevalence of MA in those children who were older than 10 years but this apparent increase of microalbuminuria was not significant. This increase with age was also noted in other studies[11,18, 19]and may possibly be as a result of higher number of crisis in these children and disease progression over time.

The mean haemoglobin in subjects with SCA with proteinuria was significantly lower than controls with proteinuria and lower than in subjects with SCA without proteinuria. The lower levels of haemoglobin in sickle cell anaemia subjects may signify the increased severity of the disease due to resultant sickling which in turn triggers release of prostaglandins and nitric oxide which cause oxidative damage to the glomerulus, renal vasodilatation and raised glomerular filtration rate (GFR), also anaemia will result in increased cardiac output.[20,21, 22,23]

Weight and blood pressure were not associated with the occurrence of proteinuria in subjects with SCA. However, weight was a factor in controls with proteinuria as they had a significantly higher weight than those without proteinuria. Previous studies have linked proteinuria with raised body mass index (BMI) and obesity[24,25], identifying obesity as a major risk factor to renal disease.[25] Eke *et al*[14] found significantly raised BMI in the control group with MA but BMI was not found to be significant in SCA group with microalbuminuria. Microalbuminuria found in SCA, occurs independent of the other known factors influencing the prevalence of renal disease in the control population.

Even though the study found twice as many children with SCA having haematuria, the prevalence of haematuria in SCA subjects in this study may be clinically significant and it is possible that increasing the sample size of subjects in this study will increase the power to detect differences between the two groups. Some older studies done decades ago showed lower prevalence of haematuria[26,27] Konotey-Ahulu[26] recorded a prevalence of 2.1% in sickle cell anaemia subjects with haematuria at the Korle Bu hospital, Ghana. Aikhionbare *et al*[27] did not find haematuria in the 101 subjects with SCA or the controls then studied in Zaria. Both studies like this study did not find a significant difference in the occurrence of haematuria between subjects with SCA and HbAA controls. The higher prevalence of haematuria found in this study compared to the studies by Konotey-Ahulu[26] and Aikhionbare[27] may be as a result of the long time that has elapsed between their studies and this study allowing for other factors leading to increasing prevalence of renal disease noted worldwide, such as increased sensitivity of test materials and changes in lifestyle. Ugwu *et al*[9] in Port Harcourt reported a higher prevalence of haematuria of 11.1% [9] while Anigilaje *et al*[28] in Ilorin studied 75 subjects with SCA in their steady states and reported prevalence of haematuria of 13.3%.[28] While dipstix method was used in Port Harcourt,[9]Anigilaje *et al*[28] used urine microscopy in addition to urine diptix. The results obtained by Anigilaje *et al*[28] were higher than what was recorded in this study and in the study by Ugwu *et al*,[9]as this may be as a result of the urine sediment microscopy method used in the Ilorin study as against urine dipstix used in the latter two studies.

There was no significant sex predilection for haematuria among subjects with SCA in this study though there was a female preponderance. This was similar to the pattern found in the controls in this study. Also, Anigilaje *et al*,[28] and Konotey-Ahulu[26]found no significant sex predilections in their studies. Female preponderance may be explained on the background of the anatomy of the female genitalia which predisposes the urethra to trauma and ascending infections that may lead to transient occult haematuria.[13]Studies have also shown the prevalence of renal papillary necrosis which is a cause of haematuria was commoner in females.[29,30] This study noted an apparent increase of haematuria with age similar to previous studies.

The estimated glomerular filtration rate eGFR increased with age in both males and females in the SCA and control groups with no statistically significantly difference between both groups. Wigfall *et al*[11]in their study of children aged 2 to 21 years recorded a higher than expected eGFR in the SCA group in the first decade which declined toward normal in the second decade. This contrasted with the findings of this study which found the eGFR was within low to normal limits in the first decade and steadily increased with age similar to findings in controls as were also reported by Okoro and Onuwameze[31] and Olowu *et al*.[32] The presence of urinary abnormalities did not significantly affect the mean eGFR, and similar to the report by Alvarez *et al*.[33]

The lengths of the right and left kidneys in sickle cell anaemia group were significantly longer than those in the control group. This increased renal size was also documented by Odita *et al*[29] in Nigeria unlike Ibinayie *et al*[34] who found 27% of subjects with SCA had shrunken kidney. This study and Odita *et al*[29] looked at children, whereas the study by Ibinaiye *et al*[34] involved mainly adults up to 54 years[34]who may have had continuous renal damage leading to shrunken kidneys. The mean

lengths for the kidneys for the SCA and control groups where within normal range; this is similar to findings by Yeboah and Rodrigues[35] in Ghana.

Few (2.8%) of the SCA subjects had increased diffuse echogenicity/loss cortico-medullary differentiation demonstrating structural abnormalities occurring in childhood. All subjects with renal abnormalities on ultrasonography were nine years or older and all microalbuminuria though none had proteinuria or haematuria demonstrable on urine dipstix, raised blood pressure or abnormal estimated glomerular filtration rates. Other studies have shown increased prevalence of renal echogenicity in subjects with SCA this has been attributed to renal papillary necrosis, presence of high concentrations of iron deposits within tubular epithelial cells, focal scaring and interstitial fibrosis in the vasa recta system, glomerular hypertrophy and renal sclerosis.[36, 37]

Conclusion

There were significant renal glomerular function abnormalities occurring in children as low as four years. Glomerular filtration rate however appears to remain within normal. Renal structural abnormalities occur in lower percentage children with sickle cell anaemia but its association with renal glomerular function needs to be further explored.

Authors' contributions
Olorukooba AA: Conceptualization and design of study, literature search, acquisition of data, analysis and interpretation of data, drafting the manuscript and revising of intellectual content.
Akuse RM, Ogunrinde GO, Mamman AI, Yusuf R: Design of study, analysis and interpretation of data and revision of manuscript.
Kajogbola G: Acquisition of data, interpretation of data and revision of manuscript.
Conflict of interest: None.
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Recommendation

The use of routine microalbuminuria assay needs to be encouraged among children with sickle cell anaemia and renal ultrasound evaluation should be included in follow up of children with microalbuminuria.

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