ORIGINAL ARTICLE

Glomerular Filtration Rate in Homozygous Sickle Cell Disease children in Steady State and Healthy Nigerian Children: A Comparative Study in north-eastern Nigeria

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ABSTRACT

Background: Homozygous sickle cell disease (HSCD) is the most common inherited blood disorder of public health importance worldwide, with Sub-Saharan Africa accounting for a third of the global burden. The effect of HbS on the kidneys results in sickle cell nephropathy, which contributes to increased mortality among HbSS patients beyond third decade of life. Glomerular filtration rate (GFR) is an important renal function test for evaluating progress of sickle cell nephropathy, however, this is seldom done to HbSS patients especially in the insurgency that devastated the North-eastern part of Nigeria, where displacement of people has led to increase in diarrhoeal diseases with its complications which also contributes to renal diseases, hence the need for this study. **Objective**: To determine the baseline glomerular filtration rate of homozygous SCD in steady state and compare same with normal controls. **Methods:** This is a prospective comparative study conducted at the University of Maiduguri Teaching Hospital (UMTH). The study population consisted of age and sex matched HbSS subjects in steady state and children with haemoglobin AA genotypeaged 3-14 years. The study was conducted over a period of 6 months. Anthropometry and serum creatinine of the subjects were determined and GFR calculated using Schwartz formula. **Results:** Two hundred and twenty children consisting 110 HbSS and 110 controls were enrolled. This consist of 106 males and 114 females with M:F ratio of 0.9:1. Mean ages of HbSS patients and HbAA subjects were 8.2years and 7.9 years respectively. The mean GFR (SD) was 125.9 (31.9) ml/min/1.73m^2 and 93.0 (16.1) ml/min/1.73m^2 for the HbSS and HbAA controls, the difference between the means was significant (P<0.001). The normal GFR range for the controls was 77 to 109 ml/min/1.73m^2. Sixty-seven (61%) casesand 86 (78%) controls had GFRs within normal range. There was statistically significant difference for GFRs above and below the normal range (Z-score=6.2 & -2.9, p<0.001 & p<0.004). **Conclusion:** About a third of HbSS children in steady state have elevated GFR, this suggests the presence of moderate renal pathology. Regular monitoring of these children will lead to improvements in management of sickle cell nephropathy and their quality of life.

Keywords: Glomerular filtration rate, homozygous, sickle cell disease, steady state, children.

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Access this article online

QuickResponse Code

website:www.bornomedicaljournal.com

DOI: 10.31173/bomj.bomj_192_17

Introduction

Homozygous sickle cell disease(HSCD) is the most common inherited blood disorder of

growing public health importance worldwide.[1]

It has been established that about 300,000 HSCD children are born every year, and 75% of them are in Sub-Saharan Africa.[2]It is a multisystemic disorder affecting almost all organs of the body including the kidneys as result of the combined effects of chronic anaemia, recurrent infections, chronic hypoxia and repeated infarction.[3]

Both structural and functional renal abnormalities termed sickle cell nephropathy are widely reported complications of sickle cell anaemia.[4-13] Sickling of the red blood cells (RBCs) in the renal medulla is particularly common, with consequent effects of decreased medullary blood flow, ischaemia, micro infarction and papillary necrosis, these result in the dilatation of the renal pelvis capillaries and veins. Children with HbSS beyond the age of five years may develop progressive impairment of their renal function due to sickling of red blood cells in the renal medulla. Increase glomerular filtration rate (GFR) is particularly common in children with HbSS.[9,12,14,15]

Renal functional abnormalities are clinically evident as impaired urinary concentrating ability (a condition termed as hyposthenuria), impaired acidification of urine and abnormalities of potassium excretion.[9,10,16]Though majority of children with HbSS die from infectious diseases, deaths from chronic kidney disease (CKD) becomes more prevalent after the third decade of life.[11,17] Glomerular filtration rate estimation is an important test of renal function, and for evaluating progress of kidney disease in HbSS children.[14]

Most prospective studies conducted on renal functional assessment using the GFR in Nigerian children with HbSS are from Southern and EasternNigeria.[18-23] There are few published data on baseline renal function in children of the North-East region of Nigeria.[15] The region has the highest frequency of the Hb AS in Nigeria with 32.7% and 27.9% among the Bades and Kanuris of Yobe and Borno States respectively.[24]The outcome from this study is expected to add to the lean database on the subject matter.

The main objective of this study was to assess renal function using GFR in steady state HbSS children in the north eastern region of Nigeria by using the height/serum creatinine ratio.

Materials and Methods

This prospective study was conducted at the University of Maiduguri Teaching Hospital, Maiduguri, over a six-month period, after obtaining clearance from the Hospital's Ethical Committee (ADM/TH/75/Vol.III). An informed written consent was obtained from the subjects and parents/guardians. Verbal assent was also obtained from children 7 years and above.A minimum sample size of 97 was determined using Taylor's formula[25] and 'p' was taken from a previous study.[26] However, 110 children aged 3-14 years with homozygous SCD in steady state and 110 children with haemoglobin AA genotype were enrolled. The homozygous SCD children in a steady state as defined by *Akinola et al*,[27]were drawn from those attending the Paediatric Sickle cell clinic at the University of Maiduguri Teaching Hospital, when they met the inclusion criteria. Such children presented with no complaints, were free from any form of crisis for at least two weeks, and have not had blood transfusion over the last three months.After history-taking and examination they were given routine folic acid, proguanil antimalarial prophylaxis and penicillin V for the under-fives who have not had pneumococcal conjugate vaccine. The

controls were age and sex matched healthy children with haemoglobin AA on follow up after recovery from minor ailments at the General Paediatric Outpatient Clinic of the hospital. Children under 3 years were excluded from the study because of the known variation in GFR in early childhood.[28]

The standing height in (cm) and weight in (kg) were measured using Wunder'sstadiometer fitted with a weighing scale. The height was measured with subject bare-footed, heels back and occiput in contact with the stadiometer back support. Each subject was also weighed with minimal clothing as possible with measurement to the nearest 0.5 gram with the pointer adjusted for zero error. The weighing scale pointer was readjusted to the zero mark before each measurement and a standard weight of 5kg was used to readjust the scale at the beginning of every day of the clinic.

The axillary temperature was measured using a digital thermometer left in place until it stops blinking after about two minutes. Body surface area was read off a standard normogram using age (years), weight and height previously measured.

Following these, 3mls of blood was drawn using aseptic technique, from the most obvious peripheral vein on the dorsum of the hand or the forearm of each subject and collected into a lithium heparinised bottle for estimation of serum creatinine level. Each batch of blood sample collected per clinic session was analysed for serum creatinine on the same day, by a laboratory scientist the chemical pathology laboratory of UMTH, using standard method of Heinegard and Tiderstrom.[29]This is a direct method and does not involve treatment of the serum with Fuller's earth or Lloyd's reagent; thus, interfering chromogens present are eliminated by the use of sodium dodecyl sulphate (SDS).

Glomerular filtration rate was determined by use of the height/serum creatinine ratio, Schwartz formula,[30]a method which despite its limitations[31,32] is suitable for routine clinical work in our setting; because of the advantages of rapid determination, reasonable accuracy and the avoidance of 24hours urine collection justify the use of this formula in the setting of paediatric practice in resource limited setting.

The GFR (expressed as ml/min/1.73m^2) was calculated using the height/serum creatinine ratio, Schwartz formula.[30]

$$\text{GFR (ml/min/1.73m}^2) = \frac{C\ x\ height\ in\ cm}{creatinine\ in\ mg/100\ ml}$$

C represent a constant, which is taken as 0.55 for children and girls. While 0.7 for adolescent males' ≥ 13 years, S_{cr}represent serum creatinine, while 1.73m^2 is the standard adult BSA. A normal GFR range of 86 to 130ml/min/1.73m^2 (3-14yrs) was used.[19]

Packed cell volume was measured at the Side-Laboratory of the Emergency Paediatric Unit (EPU) of UMTH.

Data obtained were analysed using Statistical Package for Social Sciences (SPSS) version 16 of 2008 (SPSS, Chicago, Illinois, USA). Continuous data were expressed as mean ± SD. Student's t-test was used to test for significance difference between the means; while Z-score for 2 population proportions was used to compare the differences between numbers of HbSS children with GFR outside the normal range and those of control children; values of $p<0.05$ were considered significant.

The Pearson's correlation test was used to test for the presence of correlation between GFR and PCVs in HSCD patients.

Results

The age, gender and haemoglobin genotype distribution of the 220 subjects studied are shown in table 1. There were equal numbers of steady state HbSS and HbAA subjects. There were 106 males and 114 females with M:F ratio of 0.9:1. The male to female ratio for steady state HbSS subjects was 1.08:1 (57 males and 53 females), and 0.8:1 (49 males and 61 females) for the control subjects. The age range was same for both groups; the mean age of HbSS subjects was 8.2yrs and that of HbAA controls was 7.9yrs. There were no significant differences between the mean ages of HbSS subjects and HbAA controls (P>0.05).

Anthropometric indices of the study subjects are as presented in table 2.

There was consistent increase in mean weights and heights across the age groups for both study subjects. The mean weight for the HbSS subjects was higher than in control in age groups 3-5yrs and 6-10yrs, while the reverse was the case for age group 11-14yrs. The HbSS group had higher mean height than control group in age groups 6-10yrs and 11-14yrs, while the reverse was the case for age group 3-5yrs.

The mean body mass index (BMI) for the HbSS subjects in age group 3-5yrs was higher than in the age group 6-10yrs, there was consistent increase across the age groups for the control group. However, the mean BMI for HbSS subjects were higher than those ofthe control in age groups 3-5yrs and 6-10yrs, the reverse was the case for age group 11-14yrs.

The mean haematocrit of the HbSS subjects was 22.3 ± 2.3, while it was 33.5 ± 2.5 for the controls, the difference was statistically significant (P<0.001). There was a negative correlation between GFR and haematocrits in the HbSS patients (P>0.450; r = -0.007).

The mean GFR was 125.9 (31.9) ml/min/1.73m^2 for the HbSS group and 93.0 (16.1) ml/min/1.73m^2 for the control group, the difference between the means was significant (P<0.001) (Table 3).Differences between the means was significant across all age groups.

The GFR range from present study for control children was 77 to 109 ml/min/1.73M^2.

Sixty-seven (61%) HbSS and 86 (78%) HbAA control children had GFRs that were within normal range. Table 4 compares the number of HbSS children and HbAA controls with abnormal GFR values. The comparison yielded significant difference for GFRs above and below the normal range (Z-score=6.2 & -2.9, p<0.001 &p<0.004) respectively.

Table 1: Age, Gender and Hb Genotype Distribution of the Study Population

Age group (years)	HbSS		Control		Total
	Male n (%)	Female n (%)	Male n (%)	Female n (%)	
3 – 5	18 (31.6)	13 (24.5)	15 (30.6)	16 (26.2)	62 (28.2)
6 – 10	10 (17.5)	14 (26.4)	18 (36.7)	31 (50.8)	73 (33.2)
11 – 14	29 (50.9)	26 (49.1)	16 (32.7)	14 (23.0)	85 (38.6)
Total	**57 (51.8)**	**53 (48.2)**	**49 (44.5)**	**61 (55.5)**	**220 (100)**

TABLE 2: Anthropometric indices of the study population

Anthropometric Indices	Age Groups (Years)					
	3-5		6-10		11-14	
	HbSS N=31	HbAA N=31	HbSS N=24	HbAA N=49	HbSS N=55	HbAA N=30
Weight, kg						
Mean (SD)	15.3(3)	15(3.7)	21(7.1)	20.7(5)	34.7(9.2)	36.3(9.2)
Height, cm						
Mean (SD)	100(6.6)	105.7(10)	121.1(13.9)	121(10.8)	146.4(9.8)	145.4(6.6)
BMI, kg/m²						
Mean(SD)	15.2(2.5)	13.1(1.6)	14.0(2.9)	13.9(1.4)	16.2(3.2)	17.4(3.2)

TABLE 3: Mean Glomerular Filtration Rate in HbSS and Normal Control Children

Age group (years)	Mean ± SD, ml/min/1.73M²				
	HbSS	N	CONTROLS	N	P
3 – 5	112 ± 24	31	94 ± 17	31	<0.001
6 – 10	126 ± 33	24	92 ± 13	49	<0.001
11 – 14	134 ± 33	55	93 ± 20	30	<0.001
3 – 14	126 ± 32	110	93 ± 16	110	<0.001

TABLE 4: Comparison between Number of HbSS and Control Children with GFR Outside Normal Range.

Normal GFR Range[a]	Number of Subjects with GFR outside normal range		Z-score	P
	HbSS [N=43]	Controls [N=24]		
Above	35(81.4)	1(4)	-2.9	<0.004
Below	8(18.6)	23(96)	6.2	<0.001

[a]77 to 109 ml/minute/1.73M² (3-14 years).
Figures in parentheses represent percentages.

Discussion

The finding of higher mean GFR in the HSCD compared to control children in this study is consistent with the findings of Hatch *et al,*[33] Oyinade,[20] as well as Addae and Addae.[34] Similar findings were also reported by the much cited earlier works that demonstrated increased GFR in HbSS children from West Indies and North America.[9,35] However, the finding of significantly higher mean GFR in steady state HbSS children as compared to healthy controls in this study is at variance with works of Olowu*et al*,[14] Okoro and Onwuameze,[19] Aikhionbare *et al*.[21]Similarly our finding is at variance with the early work on GFR in children with HSCD by Calcagno *et al*.[36]Thiosulphate clearance method was used by Calcagno to study GFR in five children with HbSS and a reduced GFR value was found. The small sample size used by Calcagno may probably be due to the cumbersome nature of the analytic technique. Notwithstanding the small number of subjects studied may have contributed to the finding of reduced GFR, if an appropriate sample size was used the finding might have probably been different. Early renal function changes is seen in HSCD patients because of the increase in the renal cortical blood flow (RBF) and GFR that results from altered glomerular auto regulatory mechanism,[37]and prostaglandinsmediating afferent arteriolar vasodilatation.[13]Furthermore, there is enlargement in the glomerular size and it is postulated that increase glomerular perfusion leads to the enlargement of the glomerulus.[13,38] The increase in RBF and GFR result from increased sludging of red blood cells in the microcirculation due to chronic low oxygen tension. This leads to ischaemia and micro infarctions, which result in an increased production of renal vasodilatory prostaglandins leading to vasodilatation and hyperfiltration in the glomeruli.[37,38]All these increase in glomerular size, RBF and GFR were reported to start after the age of 2 years.[7,39]Based on the findings of higher GFR in the HbSS subjects in this research that might have resulted from early hyperfiltration that lead to possible glomerular enlargement is therefore, reasonable to suggest that the glomerular changes in SCD are haemodynamically mediated. The consistent increase in GFR with age among the HbSS subjects observed in this study is consistent with the previous findings that showed positive correlation between age and GFR for children with HSCD.[40-44]This finding is however, at variance with the findings of Olowu*et al,*[14]Okoro and Aikhionbare*et al*.[21] Olowu showed that no significant differences exist between different age groups while Aikhionbare found higher mean endogenous creatinine clearance in younger HSCD children aged between 1 and 4 years, the difference was however, not significant. This varying finding on the effect of age on GFR could be attributed to small sample size of 22 in case of Aikhionbare. The reason for the finding in the work by Olowu with appropriate sample size is not clear.Earlier reports showed significant and progressive fall in GFR with age occurring in SCD and even normal individuals from 20 years of age[39,45] onward and severely low GFR levels have also been reported in some adults with SCD[39,46] hence, progressive renal insufficiency may be a significant cause of morbidity and mortality in older patients with HSCD.[47]

Our research was not without limitations, samples were collected in steady state and only once. Patients with low GFR may have had acute kidney injury. Interventional study

is also necessary to determine effect of interventions (such as use of low dose ACE inhibitors and hydroxyurea) on hyperfiltration and long-term outcome of renal function in HSCD patients.

Conclusion

About one third of HbSS children aged 3 to 14 years attending PaediatricHaematology clinic of UMTH have elevated GFR at steady state compared to HbAA subjects, suggesting underlying renal pathology.

Source of funding: Self-funded

Conflict of interest: None declared

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Cite this Article as: Farouk AG, Ibrahim BA, Sulaiman MM, Asheikh MM, Yusuf H, Musa AH. Glomerular Filtration Rate in Homozygous Sickle Cell Disease children in Steady State and Healthy Nigerian Children: A Comparative Study in north-eastern Nigeria. **Bo Med J 2020; 17(1): 1-9 Source of Support:** Nil**, Conflict of Interest:** None declared