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Research Article

Prevalence of urinary abnormalities amongst children with sickle cell anaemia in steady state in a tertiary hospital in Nigeria

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ABSTRACT

Aim: To determine the prevalence of urinary abnormalities among children with SCA and compare them with those of children with haemoglobin AA (HbAA) genotype.

Sudy desig: Prospective study

Place and duration of study: Data were obtained from children who attended the children outpatient clinic and haematology clinic between May 1st to August 31st 2017.

Meodology: Seventy children with SCA in steady state and 70 age and gender matched HbAA children were studied at the University of Port Harcourt Teaching Hospital (UPTH) using urine dipstick, microscopy, culture and sensitivity and estimated glomerular filtration rate (eGFR).

Resuls: The mean age of the children was 8.53 ± 4.85 years. Fifty-seven (81.4%) of the children with SCA had at least one urinary abnormality compared to only 15 (21.4%) of the controls. The prevalences of urinary abnormalities between subjects and controls were: proteinuria 21.4% versus 2.9% (p=0.0007), haematuria 5.8% versus 0.0% (p=0.0424). Children with SCA who had urinary abnormalities were seven times more likely to have decreased eGFR than those who did not have urinary abnormalities. (OR=7.54 ; 95%C.I. p=0.0476). However, no individual urinary abnormality significantly predicts abnormal renal function.

Colusion: Children with sickle cell anaemia in steady state had a significantly higher prevalence of urinary abnormalities therefore routine urinalysis during follow up visits is advocated

Keywords: Sickle cell anaemia, Glomerular filtration rate, Urinary abnormalities

INTRODUCTION

Sickle cell anaemia (SCA) is a genetic blood disorder caused by the inheritance of the haemoglobin S (HbS) gene from both parents resulting in the homozygous state (HbSS) (Serjeant GR, 2001). SCA accounts for about 25% of the under-5 mortality in Africa, with more than 16% of such deaths occurring in West Africa (DeBaun MR, 2016).

The sickle haemoglobins make the red blood cells (RBCs) crescent-shaped, more rigid and clog together eventually leading to vasoocclusion and haemolytic crises (Abbud-Filho M, 2013). Sickling of these RBCs in the kidneys especially in the medulla, cause decreased medullary blood flow, ischaemia, microinfarction and papillary necrosis which could result in renal impairment (Revuelta LK, 2011).

Sickle cell nephropathy (SCN) manifests as glomerular abnormalities (initially increased renal plasma flow then later decreased flow, proteinuria, haematuria), distal renal tubular dysfunction (hyposthenuria, impaired urinary acidification, impaired potassium excretion), and supranormal proximal tubular function (increased phosphate reabsorption, increased uric acid and creatinine secretion (Revuelta LK, 2011).

Though some earlier studies have shown that the prevalence of urinary abnormalities amongst children with SCA is higher than in those with hemoglobin AA (HbAA), none of them related these abnormalities to renal function (Ugwu RO, 2007 ; Anigilaje EA, 2013 ; Anigilaje EA, 2016 ; Osei-Yeboah CT, 2011). This study sets out to determine the prevalence of urinary abnormalities in

children with SCA who were in steady state using urine dipstick and to note its relevance in screening for renal disorders.

MATERIALS AND METHODS

This prospective comparative study was carried out in the Paediatric Haematology Clinic and Children Out Patient Clinic of the University of Port Harcourt Teaching Hospital (UPTH) over a four months period from May to August 2017. The study population were known children with Sickle Cell Anaemia (HbSS) who were in steady state (Ballas SK, 2012) (had no history of fever in the preceding four weeks, no history of painful crises that required treatment in the hospital in the preceding four weeks and no history of blood transfusion during the previous 4 months). All the children with SCA aged between 1 and 17 years who presented to the Paediatric Haematology Clinic, who gave assent and parents gave consent and who met the inclusion criteria were recruited. The controls were age and gender matched children with documented HbAA results from electrophoresis who were on follow up or treatment for minor ailments or came for school medical examination at the Children Out Patient Clinic (CHOP).

Exclusion criteria for both groups were children with severe anaemia requiring blood transfusion in the preceeding four months before the study,previous history of renal disease,females menstruating as at the time the study was done, history of ingestion of drugs such as Rifampicin (that could colour the urine red) or drugs that could decrease the reactivity of dipstick like nitrofuratoin, tetracycline and captopril in the preceeding four weeks and those who had taken non steroidal anti-inflammatory drugs or antibiotics in the preceeding week before recruitment.

The minimum sample size was calculated using the formula for comparison of proportions (Ryan TP, 2013)

$$n = \frac{\left\{(Z\alpha + Z\beta)^2 (p_1 q_1 + p_2 q_2)\right\}}{(p_1 - p_2)^2}$$

Where,

n=minimum sample size for each group

Zα=critical value of the Normal distribution with confidence interval of 95%=1.96

Zβ=critical value of the Normal distribution with power of 90%=1.282

Power of the study set at 90% (Araoye MO, 2003)

p1=proportion of proteinuria in sickle cell anaemia5=20.8%=0.208

p2=proportion of proteinuria in haemoglobin AA5=1.4%=0.014

q1=1-p1=1-0.208=0.792

q2=1-p2=1-0.014=0.986

$$n = \frac{\left\{(1.96 + 1.282)^2 (0.208 \times 0.792 + 0.014 \times 0.986)\right\}}{(0.208 - 0.014)^2}$$

n=49.368

The calculated minimum sample size was 50.

Ethical clearance was obtained from the Research and Ethics Committee of UPTH. A written informed consent was obtained from parents/guardian of the selected subjects. All the children found to have significant urinary abnormalities were referred to the Nephrology Unit for further evaluation of renal function and follow up.

A semi-structured interviewer administered questionnaire was administered to each recruited child. Biodata, history of previous episodes of crises, previous history of blood transfusion and drug history were obtained.

The height was measured with a stadiometer (Seca® model 0123). The blood pressure was measured after patient was allowed to rest for 5 mins using Accoson® mercury sphygmomanometer with appropriate sized cuff bladder that covered two-third of the length of the child's upper arm and encircled 80% of the arm circumference.

Each child was given a properly labeled sterile universal bottle in the clinic to collect about 10 mls of midstream clean catch urine. Approximately 5 mls was turned into another sterile universal bottle for dipstick urinalysis while the remaining 5 mls was sent to microbiology laboratory for urine microscopy, culture and sensitivity. Dipstick urinalysis was done using Medi-Test Combi 10® SGL urinalysis reagent strip with batch no LCB 0339-01 which is able to test for protein, blood, nitrite, leucocytes, specific gravity, pH, bilirubin, urobilinogen, glucose and ketones.

The following criteria were used to define significant urinary abnormalities.

Proteinuria-Presence of protein in the urine of 1+(30 mg) or greater on dipstick urinalysis

Haematuria-Presence of 1+ of blood in urine or greater on dipstick urinalysis

Leucocyturia-Presence of white blood cells of 1+or greater in the urine on dipstick urinalysis

Hyposthenuria-Specific gravity of urine less than 1.010 on dipstick urinalysis

Poor urine acidification-Urine pH of 7.0 and greater on dipstick urinalysis.

About three millilitres of venous blood was collected into the lithium heparin bottle for serum creatinine estimation in umol/L using the Jaffe-Slot method (Slot C, 2009).

Glomerular filtration rate (GFR) in mls/min/1.73 m^2 was calculated using the revised Schwartz formula (Schwartz GJ, 2009).

$$GFR = \frac{k \times Ht}{Cr_{serum}}$$

Where

Ht=height in cm

k=constant 0.413

Cr_{serum}=serum creatinine in mg/dl

(Serum creatinine was converted from umol/l to mg/dl by dividing by 88.4)

Glomerular filtration rate <90 mls/min/1.73 m^2 indicates reduced renal function. GFR less than 60 mls/min/1.73 m^2 indicates significantly reduced renal function (Vogt BA, 2016).

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 20.0 software. Categorical variables were analyzed using the Chi square test or Fischer's exact test. Confidence interval was set at 95% and a p value of ≤ 0.05 was considered significant.

RESULTS

There were 38 (54.3%) males and 32 (45.7%) females in each group with a male to female ratio of 1.2:1. The age range was from 1 to 17 years with a mean age of 8.53 ± 4.85 years for both groups. Children aged 1-5 years were 24(34.3%), 6-10 years were 21(30.0%), 11-15 years were 18(25.7%) and above 15 years were 7(10.0%) in each group.

Table 1 shows the prevalence of urinary abnormalities amongst the subjects and controls. Fifty seven (81.4%) of the subjects had at least one urinary abnormality compared to 15(21.4%) of the controls. Forty three (61.4%) of the subjects and eight (11.4%) of the controls, had more than one urinary abnormalities. The difference in proportions was statistically significant (p=0.0001).

Table 1. Prevalence of urinary abnormalities amongst the subjects and controls

Urine abnormalities	Subjects n(%)	Controls n(%)	Total n(%)
None	13 (18.6)	55 (78.6)	68 (48.6)
One	14 (20.0)	7 (10.0)	21 (15.0)
Two	29 (41.4)	5 (7.1)	34 (24.3)
Three	8 (11.4)	3 (4.3)	11 (7.8)
Four	5 (7.2)	0 (0.0)	5 (3.6)
>Four	1 (1.4)	0 (0.0)	1 (0.7)
Total	70 (100.0)	70 (100.0)	140 (100.0)
Fisher's exact test=55.805; p-value=0.0001*; *=significant			

Table 2 shows the prevalence of the different abnormalities among the children with SCA and the controls. The prevalence of all these urinary abnormalities were higher amongst the subjects than the controls. The differences in the prevalences of each of the urinary abnormalities between the subjects and controls were significant except for leucocyturia and poor acidification of urine.

	Subjects	Controls	Total		
Variables	**N=70 n(%)**	**N=70 n(%)**	**N=140 n(%)**	**Chi square/ Fisher's exact test**	**p-value**
Proteinuria					
Negative/ Trace	55 (67.6)	68 (97.1)	123 (87.9)		
Positive	15 (21.4)	2 (2.9)	17 (12.1)	11.870**	0.0007*
Haematuria					
Negative/ Trace	66 (94.3)	70 (100.0)	136 (97.1)		
Positive	4 (5.7)	0 (0.0)	4 (2.8)	4.12**	0.0424*
Leucocyturia					
Negative/ Trace	34 (48.6)	61 (87.1)	95 (67.9)		
Positive	36 (51.4)	3 (12.9)	18 (32.1)	35.39**	2.68
Nitrite					
Negative	49 (70.0)	65 (92.9)	114 (81.4)	12.092	0.0005*
Positive	21 (30.0)	5 (7.1)	26 (18.6)		
Specific gravity					
1.000-1.009	13 (18.6)	2 (2.9)	15 (10.7)	9.03**	0.0026*
1.010-1.030	57 (81.4)	68 (97.1)	125 (89.3)		
Urine pH					
≤ 7	37 (52.9)	47 (67.1)	84 (60.0)	2.97	0.0844
>7	33 (47.1)	23 (32.9)	56 (40.0)		
*Statistically significant **Fisher's exact test					

Table 2. Prevalence of Proteinuria, Haematuria, Leucocyturia, Nitrituria, Hyposthenuria or Poor Acidification of urine among the subjects and controls

The findings on microscopy for the subjects and controls were as follows: red blood cells (4.3% vs. 1.4%), white cell casts (2.9% vs. 0.0%), pus cells (7.1% vs. 1.4%), crystals (5.7% vs. 0.0%), and epithelial cells (42.9% vs. 22.9%) respectively. Escherichia coli was the most common

organism isolated amongst the subjects while amongst the control, the three organisms had equal prevalence (Figure 1). All those with bacteria growth had leucocyturia and nitrituria. The bacteria organisms were sensitive to ceftriaxone, amoxicillin, nitrofuratoin but resistant to cefuroxime and cotrimoxazole.

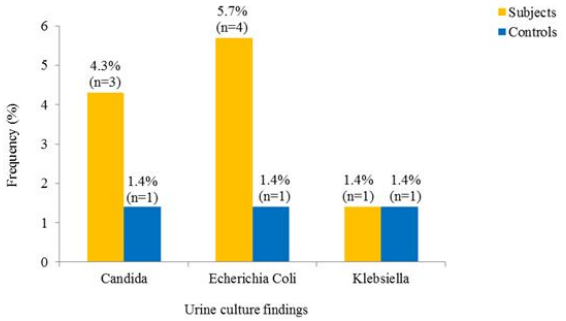

Figure 1. Organisms isolated in urine culture in subjects and controls of the study

The mean eGFR for the subjects was 104.26 mls/min/1.73 m^2 while that of controls was 105.94 mls/min/1.73 m^2. Twenty-three (32.9%) of the subjects had decreased eGFR (<90 mls/min/1.73 m^2) compared to eight (11.4%) of the control (Fisher's exact test=21.427; p-value=0.0001). No child in both groups had eGFR<15 mls/min/1.73 m^2 (Table 3).

Table 3. Estimated glomerular filtration rates of subjects and controls in the study

	Subjects	Controls	Total		
eGFR(mls/min/1.73 m^2)	**N=70 n(%)**	**N=70 n(%)**	**N=140 n(%)**	**Fisher's exact test**	**p-value**
>120	23 (32.9)	11 (15.7)	34 (24.3)		
90-120	24 (34.3)	51 (72.9)	75 (53.6)	21.427	0.0001*
60-89	18 (25.7)	7 (10.0)	25 (17.9)		
30-59	4 (5.7)	1 (1.4)	5 (3.6)		
15-29	1 (1.4)	0 (0.0)	1 (0.7)		
*Statistically significant					

Table 4 describes the relationship between urinary abnormalities by urine dipstick and eGFR for subjects. Twenty two (38.6%) of the subjects who had urinary abnormalities, also had decreased eGFR while only one (7.7%) of the subjects who did not have any urinary abnormality had decreased eGFR. (p=0.048). Children with SCA who had urinary abnormalities have a 7.54 chance of having decreased eGFR than those who did not have urinary abnormalities (odd ratio 7.54).

Table 4. Relationship between presence of urinary abnormalities and estimated glomerular filtration rate of subjects

Estimated Glomerular Filtration Rate			
Urinary abnormality	**>90 mls/min/1.73 m^2 n(%)**	**<90 mls/min/1.73 m^2 n(%)**	**Total n(%)**
Present	22 (38.6)	35 (61.4)	57 (100.0)
Absent	1 (7.7)	12 (92.3)	13 (100.0)
Total	23 (32.9)	47 (67.1)	70 (100.0)
Odds ratio (95% Confidence interval): 7.54 (1.15-62.171) Fisher's exact p-value=0.0476* *Statistically significant			

Table 5 describes the relationship between the different urinary abnormalities by urine dipstick and eGFR for subjects. Most of those who had urine abnormalities had estimated GFR greater than 90 mls/min/1.73 m^2. None of the individual urine abnormality had direct relationship to decreased eGFR.

Table 5. Relationship between different urinary abnormalities and estimated glomerular filtration rate of study subjects

Estimated Glomerular Filtration Rate					
Urine abnormalities by strips	**<90 mls/min/1.73 m^2 n(%)**	**>90 mls/min/1.73 m^2 n(%)**	**Total n(%)**	**Chi square / Fisher's exact test**	**P-value**
Proteinuria					
Present	4 (26.7)	11 (73.3)	15 (100.0)	**	0.759
Absent	19 (34.5)	36 (65.5)	55 (100.0)		
Haematuria					
Present	1 (25.0)	3 (75.0)	4 (100.0)	**	1
Absent	22 (33.3)	44 (66.7)	66 (100.0)		
Leucocyturia					

Present	14 (38.9)	22 (61.1)	36 (100.0)	1.222	0.269
Absent	9 (26.5)	25 (73.5)	34 (100.0)		
Nitrituria					
Present	10 (47.6)	11 (52.4)	21 (100.0)	2.963	0.085
Absent	13 (26.5)	36 (73.5)	49 (100.0)		
Hyposthenuria					
Present	5 (38.5)	8 (61.5)	13 (100.0)	**	0.746
Absent	18 (31.6)	39 (68.4)	57 (100.0)		
Urine pH					
Present	12 (36.4)	21 (63.6)	33 (100.0)	0.348	0.555
Absent	11 (29.7)	26 (70.3)	37 (100.0)		
** Fisher's exact test value					

DISCUSSION

This study showed that urinary abnormalities occurred more in children with SCA. Majority (81.4%) of the subjects had at least one urinary abnormalities with almost two-third (61.4%) of them having more than one abnormality. This finding corroborated with those of earlier studies (Ugwu RO, 2007 ; Anigilaje EA, 2013 ; Anigilaje EA, 2016 ; Osei-Yeboah CT, 2011). Repeated sickling and unsickling of RBCs in SCA results in impaired renal medullary blood flow, ischaemia, microinfarction and eventual glomerular and tubular damage (Revuelta LK, 2011) which will lead to urinary abnormalities.

A proteinuria of 21.4% in the study was similar to the prevalence noted by Ugwu and Eke (Ugwu RO, 2007) in Port Harcourt more than a decade ago but was much higher than the 6.2%, 9.4% and 8% documented by (Aloni MN, 2014) in Democratic Republic of Congo, Osei-Yeboah and Rodrigues in Ghana and Anigilaje and Adedoyin in Ilorin respectively. The study population in this present study were relatively older with mean age of 8.53 ± 4.85 years, while those in the studies by Aloni et al and Osei-Yeboah and Rodrigues had mean ages of 7.3 ± 3.3 years and 7.18 ± 3.15 years respectively. Older children with SCA are more likely to have vaso occlusive crises due to the effect of repeated sickling on the kidneys with increased urinary abnormalities (Aloni MN, 2011 ; Manwani D, 2013).

Similarly, the prevalence of proteinuria in this study was significantly higher in children with HbSS than HbAA genotypes (21.4% vs. 2.9%), a finding which was similar to what was reported by Ugwu and Eke (20.8% vs. 1.4%). It however contrasted with that of Anigilaje and Adedoy in and Osei-Yeboah and Rodrigues who did not observe significant differences in their studies (8% vs. 5%) and (9.4% vs. 8.6%) respectively. In this study, proteinuria was defined as the presence of protein of 1+ and greater in the urine while in these other studies, it was defined as the presence of trace protein and greater in the urine. Trace proteinuria can be found in many children who do not have any renal abnormality and this might be the reason why the difference between the prevalence of proteinuria in the children with HbSS and HbAA was not significant in their studies (Pais P, 2016).

The prevalence of haematuria of 5.7% using urine dipstick documented amongst the subjects in this study was similar to the report by (Yauba MS, 2014) but much lower than what was documented by other researchers (Ugwu RO, 2007 ; Anigilaje EA, 2013). In this study, haematuria was defined as presence of blood of 1+ and greater on dipstick urinalysis while Anigilaje and Adedoyin on the other hand defined haematuria as presence of trace blood and greater on dipstick urinalysis which might account for the higher prevalence observed in their study. In contrast, Osei-Yeboah and Rodrigues documented a much lower prevalence for haematuria. The children in their study were relatively younger and urinary abnormalities have been noted to increase with age (Drawz P, 2016). On urine sediment microscopy, haematuria was defined as presence of five or more RBCs per high power field in this study while Anigilaje and Adedoyin on the other hand defined haematuria as presence of two or more RBCs per high power field. This might account for the higher prevalence observed in their study.

The prevalence of haematuria amongst children with SCA was also significantly higher than that of the control group in this present study, (5.7% vs. 0.0%) as noted in some earlier reports (Anigilaje EA, 2013 ; Osei-Yeboah CT, 2011).

In this study, the prevalence of leucocyturia of 51.4% and nitrituria of 30% observed amongst the subjects was much higher than what was observed in Ghana (Osei-Yeboah CT, 2011). This might be because the subjects in the current study were children with HbSS genotype only unlike in the

Ghanaian study where children with HbSC and Hbβthal genotypes were included. Children with HbSC and Hbβthal genotypes are known to have less frequent and less severe crises, so the risk of kidney damage from repeated crises and predisposition to UTI is reduced (19).

Leucocyturia and nitrituria were more prevalent in children with HbSS than those with HbAA in this study as observed in earlier studies though their difference was not significant (Ugwu RO, 2007 ; Osei-Yeboah CT, 2011). Children with SCA have increased susceptibility to UTI due to impaired immunological state and because they usually produce dilute urine which is a good culture medium for bacteria (Ataga KI, 2000; Cumming V, 2006).

The prevalence of hyposthenuria of 18.6% noted amongst the children with SCA in this study was comparable to the 18.1% found by (Bayazit AK, 2002) but higher than 13.9% observed in Port Harcourt over a decade earlier (Ugwu RO, 2007). Though the urine samples in the study in Port Harcourt were collected in the same manner as that in this present study, the prevalence of hyposthenuria was derived from three consecutive two weekly dipstick urinalyses while the prevalence in this study was derived from a one time reading. Children were only considered to have hyposthenuria when they had specific gravity less than 1.010 in all the three dipstick urinalyses and this might account for the difference observed.

Almost half of the subjects (47.1%) in this study had poor acidification of urine. This was much lower than the 69% observed earlier in Port Harcourt (Ugwu RO, 2007). Poor acidification of urine in this study was defined as urine pH of 7.0 and greater, while in their study, it was defined as urine pH of 6.5 and greater and almost 80% of the children with poor acidification of urine in their study, had urine pH of 6.5. On the other hand, the prevalence of poor acidification of urine in this study was higher than 38.4% reported by Silva et al among adults with SCA in India (Silva JG, 2013). Urine pH was determined on the spot in this study without prior acidification of the urine unlike in their study where urine pH was determined after urinary acidification with calcium chloride. In their study, there was deliberate acidification of the urine by use of calcium chloride.

More children with SCA had hyposthenuria and poor acidification of urine than children with HbAA in this present study. This finding was consistent with findings by Ugwu and Eke (Ugwu RO, 2007). Ischaemia involving the renal medulla leads to the inability to maintain a hydrogen ion gradient, causing an incomplete form of distal renal tubular acidosis (Silva JG, 2013).

The 7.1% of asymptomatic bacteriuria reported in this present study was comparable to the 6% reported by Chukwu et al in Enugu and the 6.6% reported by Adegoke and Adegun (Chukwu BF, 2011; Adegoke SA, 2013). In children with aymptomatic bacteriuria, alteration in the host pathogen interaction may be responsible for the absence of symptoms, despite the presence of urinary pathogens. Escherichia coli was the commonest organism isolated in the urine amongst the subjects in this study and this corroborated with earlier studies that Escherichia coli was the commonest cause of UTI (Thompson J, 2007).

The mean eGFRs for the subjects in this study were normal and did not differ significantly from that of the control group. This was similar to earlier reports by Okoro et al in Enugu, Olowu et al in Ile-Ife and Ibitoye et al in Sokoto (Okoro BA, 1991 ; Olowu WA, 2002 ; Ibitoye PK, 2016).

There was a significant relationship between the finding of urinary abnormalities on dipstick urinalysis and reduced eGFR. More than a third (38.6%) of the subjects who had abnormalities in the urine by dipstick had reduced renal function. However, no particular urinary abnormality had direct relationship with reduced renal function. This contrasted with findings by Miyatake et al in Japan and Turin et al in Canada who observed that the prevalence of proteinuria was closely linked to reduced eGFR. Unlike this study that was conducted among children, the studies by Miyatake et al and Turin et al were conducted among adults and this might account for the observed difference (Miyatake N, 2011 ; Turin TC, 2013).

CONCLUSION

Children with SCA had significant urinary abnormalities when compared to children with HbAA. The presence of multiple urinary abnormalities on urine dipstick could be a pointer to serious kidney disease.

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