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Original Article

Prevalence and Determinants of Asymptomatic Bacteriuria in Children with Sickle Cell Anaemia in Jos, Plateau State, North-Central Nigeria

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ABSTRACT

Background: In sickle cell anaemia (SCA), renal dysfunction including symptomatic and asymptomatic bacteriuria (ASB) usually starts in childhood. Children with ASB need to be identified early to forestall disease progression and attendant consequences. **Objectives:** The study therefore assessed the prevalence and determinants of ASB in children with SCA and compared it to findings in apparently healthy haemoglobin AA (HbAA) counterparts. **Methods:** The study was a comparative cross-sectional study involving 136 SCA and 136 HbAA children aged 2-17 years. Urinalysis, urine microscopy and culture were performed on samples from all the participants. The diagnosis of ASB was based on urine culture. Data on socio-demographics was obtained using a pre-tested, interviewer-administered proforma. The association between the socio-demographic characteristics and asymptomatic bacteriuria was determined using Chi-square test. A p-value <0.05 was considered statistically significant. **Results:** Prevalence of ASB in SCA children was 8.1% compared to 1.5% in HbAA children. Prominent isolated organisms were *Escherichia coli* (45.5%) and *Staphylococcus aureus* (27.3%) in SCA children; and Proteus spp (50%) and Providencia spp (50%) in HbAA counterparts. The female gender was significantly associated with the occurrence of ASB (p = 0.003). **Conclusion:** The prevalence of ASB in children with SCA in Jos is high. *Escherichia coli* is the dominant organism responsible for ASB in children with SCA in Jos. Girls with SCA are more predisposed to asymptomatic bacteriuria than boys. Therefore, we recommend routine screening of children with SCA for asymptomatic urinary tract infection in order to prevent long term renal complications.

Keywords: Sickle cell disease, asymptomatic bacteriuria, urinary tract infection, Nigeria

INTRODUCTION

Sickle cell anaemia (SCA) is the commonest and most serious form of SCD with an incidence of 1 in 300 in Nigeria.[1] SCA patients are at increased risk of infections compared to the general population as a result of multiple factors such as functional asplenia, defective complement activation, micronutrient deficiency, genetic predisposition and microvascular occlusions.[2] Furthermore, reduced leukocyte function in SCA, particularly neutrophil killing ability, has been shown to correlate with clinical severity of the disease.[3]

Urinary tract infection (UTI) which could be symptomatic or asymptomatic is one of the common infections seen in SCA. It usually results from repeated microvascular occlusion causing papillary necrosis and loss of urinary concentrating and acidifying abilities which favour

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bacterial proliferation.[4-5] UTI in young children can cause cortical scarring which can lead to hypertension and end stage renal disease (ESRD).[6]

Asymptomatic UTI also known as asymptomatic bacteriuria (ASB) is defined as the presence of significant bacterial count of $\geq 10^5$ colony forming unit per millilitre (CFU/ml) in mid-stream urine specimen processed within one hour of collection in a person without clinical signs and symptoms of UTI.[7] Asymptomatic bacteriuria has been shown to be more prevalent in SCA patients when compared to their counterparts with haemoglobin AA.[8] This is probably due to impaired immunological status resulting from auto-splenectomy, as well as alterations in the host pathogen interaction which may be responsible for the absence of symptoms despite the presence of urinary pathogens.[9-10] The most frequently isolated uropathogens are *Escherichia coli*, Klebsiella spp, and Enterobacter spp.[11]

Asymptomatic bacteriuria could lead to short- and long-term outcomes of varying severity. Studies have shown that approximately one third of girls with ASB experience resolution within weeks to months if not treated. In about 24-80% of treated or untreated cases, persistent infection or re-infection with new species is observed months later.[12] About 10% of these asymptomatic infections also become symptomatic subsequently.[13]

Plateau State where Jos University Teaching Hospital (JUTH) is located has a near temperate climate and low temperatures.[14] These environmental factors are known triggers of recurrent hypoxaemia and sickling which can lead to papillary necrosis and hyposthenuria, thereby putting SCA children in Plateau State at a probable higher risk of urinary tract infection (UTI).

This study therefore sought to determine the prevalence of ASB and its determinants in children with SCA seen at the JUTH.

METHODOLOGY

Study location

The study was conducted at the Heamatology Clinic in the Paediatric Out-Patient Department (POPD) of JUTH in Jos, Plateau State, Nigeria while the controls were selected from day-care centres, primary and secondary schools in Jos. The Jos University Teaching Hospital (JUTH) is the largest hospital in the State, and it is a 600-bed facility that provides emergency, outpatient and inpatient services in all clinical areas and laboratory services, to the State Capital, its environs and its neighbouring states.

Study Design

This is a comparative cross- sectional study conducted to determine the prevalence of ASB and its determinants among children with SCA.

Study Population

This consisted of SCA children aged 2 to 17 years who were in steady state (i.e. not in any form of crises, not suffering from any acute illness and stable for at least 4 weeks prior to being evaluated)[15] and attending the Heamatology Clinic during the study period. And apparently healthy age and gender matched children without SCA attending Day-care centres, nursery, primary and secondary schools in Jos.

Exclusion Criteria in Subjects and Controls

1. Subjects with symptoms referable to UTI e.g. fever, dysuria, enuresis, frequency or supra pubic pain.
2. Subjects with co-existing disease states capable of causing enhanced risk for asymptomatic bacteriuria independently such as diabetes mellitus, nephrotic syndrome, acute glomerulonephritis (AGN), HIV, Cerebral palsy and prolonged steroid use.
3. Subjects and controls with history of use of antibiotics two weeks prior to being evaluated as this could interfere with culture yield of uropathogens.
4. Menstruating female adolescent subjects and controls. (due to the risk of contamination which may influence the prevalence of urinary symptoms).
5. Subjects and controls who had recent history (<1 week) of manipulative urogenital instrumentation (like catheterization and cystoscopy as they could be unduly predisposed to UTI).

Sample size determination

The minimum sample size shall be determined using the formula for comparing two proportions.[16]

$$n = \frac{(Z\alpha + Z\beta)^2 \, (p1\,(1-p1) + p2\,(1-p2))}{(p1-p2)^2}$$

Where:

n = minimum sample size in each group

Zα=standard normal deviate corresponding to 5% level of significance (2 sided) = 1.96

Zβ= standard normal deviate corresponding to a power of 80% = 0.84

p1= proportion with asymptomatic bacteriuria in the control group = 4.3% =0.043 (prevalence of UTI in a previous study done in Jos) [17]
p2 =proportion with asymptomatic bacteriuria in SCA group =14.6% = 0.146(prevalence of ASB in a previous study done in Lagos) [18]

Thus,

$$n = \frac{(1.96+0.84)^2 \times (0.043(1-0.043) + 0.146(1-0.146)}{(0.043-0.146)^2}$$

$$= \frac{7.84 \times 0.1658351}{0.010609}$$

=123

Ten percent of the calculated value was added to accommodate subjects with incomplete responses and spillage of samples, therefore a total of 136 children with SCA and 136 age and gender matched apparently healthy controls were studied, with a minimum of 272 participants enrolled in the study.

Sampling Technique

SCA subjects who met the inclusion criteria were consecutively recruited until the desired sample size was obtained. An average of 20 patients were recruited per week for both the subjects and controls respectively.

For each recruited SCA subject, an eligible control with normal haemoglobin AA (confirmed by haemoglobin electrophoresis) who met the inclusion criteria were recruited using the multistage sampling technique.

Urine collection and culture

Aseptically collected mid-stream urine specimens (MSUs) was obtained in a universal sterile bottle on spontaneous voiding after observing standard precautions in urine sample collection.[19]The urine samples were transported to the laboratory in an insulated ice box within half an hour to one hour of collection. Urine culture was performed using the standard semi-quantitative culture method described by Guttmann and Stoke.[20] Bacterial culture and the developed colonies were counted using a colony counter to detect significant bacteriuria. More than 100,000 organisms/ml resulting colonies were identified according to standard methods of identification. Samples that yielded pure bacterial growth of 10^5 or more CFU per millilitre were regarded as positive yield for significant bacteriuria. Counts $\leq 10^4$ were regarded as negative. Mixed growths (growth of more than one species in a sample) especially growth of normal skin flora, were regarded as contaminants. A second urine sample was collected after 48hrs from children with significant growth and those whose second urine samples yielded significant bacterial growth of the same organism were regarded as having confirmed asymptomatic bacteriuria.

Ethical consideration

Ethical clearance to conduct the study was obtained from the Jos University Teaching Hospital Human Research Committee and the Plateau State Ministry of Education.

Written informed consent was obtained from the parents/guardians of the subjects and the controls through the various class teachers. Assent was obtained from children aged ≥10 years following explanations on the purpose of the study, use of materials gathered, and confidentiality of the information collected. To ensure the confidentially of the participants, only specific codes were used on the forms and not names.

Data/statistical analysis

All data obtained were processed and analyzed using SPSS version 23. Qualitative variables such as gender, age group in years, socio-economic status of the family and prevalence of asymptomatic bacteriuria were presented in tables as frequencies and percentages. Median and interquartile range were used as summary indices for age of the children in view of the fact that it was skewed, and Mann Whitney U test was used as a non-parametric test of difference of median age between the subject and control groups respectively.

Chi square test was used as test associations between the socio-demographic characteristics of the subject and control groups as well as for significant bacteriuria between the subject and control groups. Furthermore, association between the socio-demographic characteristics and asymptomatic bacteriuria within each of the groups was determined using Chi square statistical test. A 95% confidence interval was used in this study with a probability value of less than 0.05 considered statistically significant.

RESULTS

Socio-demographic characteristics of the study population

Two hundred and seventy-two children aged 2 to 17 years were recruited in the study. They comprised 136 sickle cell anaemia patients (subjects) and 136 age and gender matched HbAA controls. Subjects and controls were each grouped by age into 2-5 years, 6-9 years, 10-13 years and 14-17 years. There were 70 (51.5%) males in the subject group while the control group had 69(50.7%) males. The median ages of the subjects and controls 8.5 years (range: 5-12years) and 8.0 years (range: 5-13years) respectively and did not differ significantly (p= 0.969). Eighty (29.4%) of the study population were between the ages 2 and 5 years while forty-six (16.9%) were between ages of 14 and 17 years. (Table I)

Table I: Socio-demographic characteristics of the study Population

Variables	Subjects Cases (n=136) n (%)	Control (n=136) n (%)	χ^2/u	*p*-value
Gender				
Male	70(51.5)	69(50.7)		
Female	66(48.5)	67(49.3)	0.02	0.903
Age group(years)				
2-5	40(29.4)	40(29.4)		
6-9	37(27.2)	37(27.2)		
10-13	36(36.5)	36(36.5)		
14-17	23(16.9)	23(16.9)	0.00	1.00
Median age (IQR)	8.5(5-12)	8.0(5-13)	9223*	0.969
Socio-economic status				
Low	79(58.1)	79(58.1)		
Middle	31(22.8)	34(25.0)		
Upper	26(19.1)	23(16.9)	0.32	0.851

* Mann Whitney- U test, IQR- interquartile range

Table II: Prevalence of asymptomatic bacteriuria in the study population

Significant bacteriuria	Cases n (%)	Control n (%)	Total n (%)	x^2	p-value
Positive	11 (8.1)	02 (1.5)	13(4.8)		
Negative	125 (91.9)	134 (98.5)	259(95.2)		
Total	136(100.0)	36 (100.0)	272(100.0)	6.54	0.01*

**Group Chi-square: 6.54, p=0.01

Prevalence of Asymptomatic Bacteriuria in the Study Population

The prevalence of asymptomatic bacteriuria based on urine culture in sickle cell anaemia children was 8.1% compared to 1.5% in controls. Asymptomatic bacteriuria therefore occurred significantly more among children with sickle cell anaemia. (p = 0.01) Table II.

Associations Between Socio-Demographic Determinants and Prevalence of Asymptomatic Bacteriuria Among SCA Children

The prevalence of ASB among the study population in relation to socio-demographic characteristics is as shown in Table III. Of the 11 SCA subjects with asymptomatic bacteriuria, 10(15.2%) were females with just one (1.4%) male (age 14-17 years category). There was a significant association between gender and prevalence of ASB, (*p* = 0.003). Though more children with ASB (10%) were in the age group of 2 -5 years (for subjects), the age differences in prevalence were not significant (p=0.948). Among the SCA group, seven (8.9%) subjects with ASB were from low socio-economic class while 4 (15.4%) were from the upper socio-economic class. However, no significant association was found between social-class and occurrence of ASB. This is shown in Table III.

Table III: Associations between socio-demographic determinants and prevalence of ASB among SCA children

Variable	Asymptomatic bacteriuria Present n(%)	Absent n(%)	χ^2	p – value
Gender				
Male	01(1.4)	69(98.6)		
Female	10(15.2)	56(84.8)	8.61	0.003*
Age group(years)				
2-5	04(10.0)	36(90.0)		
6-9	03(8.1)	34(91.9)		
10-13	02(5.6)	34(94.4)		
14-17	02(8.7)	21(91.3)	-	0.948^f
Socio-economic status				
Low	07(8.9)	72(91.1)		
Middle	0(0.0)	31(100.0)		
Upper	04(15.4)	22(84.6)	-	0.069^f

f=Fischer exact

Association Between Socio-Demographic Determinants and Prevalence of ASB Among Controls

The two (2/136, 1.5%) children with asymptomatic bacteriuria in the control group were females. Both were from age 6 to 9 years category (4.9%) and from low socio-economic class families. There was no statistically significant relationship between gender, age and social-class and prevalence of ASB in the control group - Table IV

Table IV: Association between socio-demographic determinants and prevalence of ASB in the control group

Variable	Asymptomatic bacteriuria Present n(%)	Absent n(%)	χ^2	p - value
Gender				
Male	0(0.0)	69(100.0)		
Female	2(3.0)	65(97.0)	2.09	0.241
Age group(years)				
2-5	0(0.0)	40(100.0)		
6-9	2(4.9)	35(94.6)		
10-13	0(0.0)	36(100.0)		
14-17	0(0.0)	23(100.0)	-	0.168[f]
Socio-economic status				
Low	2(2.5)	77(97.5)		
Middle	0(0.0)	34(100.0)		
Upper	0(0.0)	23(100.0)	-	1.000[f]

Bacterial Isolates in Subjects and Controls with Confirmed Asymptomatic Bacteriuria

Figure 1 shows the proportion of the various bacterial isolates in SCA children with confirmed ASB. The most common organism isolated was *Escherichia coli* (45.5%) then *Staphylococcus aureus* (27.3%), Salmonella spp, Citrobacter spp and Providencia spp (9.1%) each.

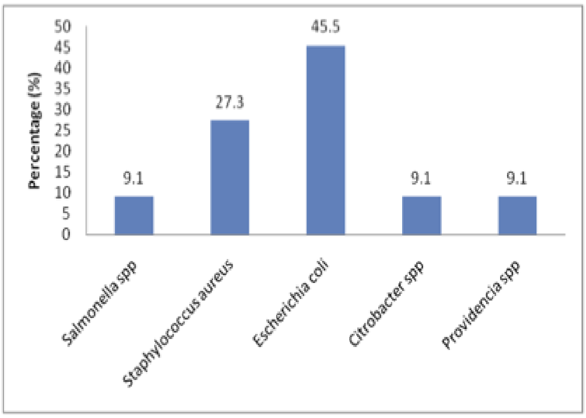

Figure 1: Bar chart showing representation of bacterial isolates in SCA children with Confirmed ASB

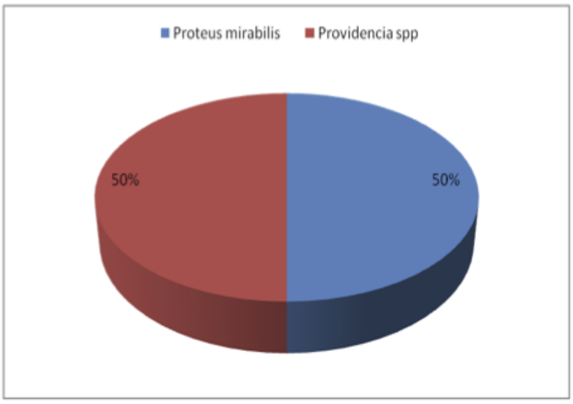

Figure 2: Pie chart displaying the bacterial isolates in non-SCA children with confirmed ASB

The bacterial isolates among non-SCA children with confirmed ASB is shown in Figure 2. The organisms isolated were *Proteus mirabilis* (50%) and Providencia spp (50%).

DISCUSSION.

The overall prevalence of asymptomatic bacteriuria in SCA children in this study was 8.1%. This value is comparable with the 7.3% reported in a previous study by Jombo *et al* [21] among Egyptian children. However, the observed rate in this study is higher than that documented in similar works carried out by Chukwu *et al* [22] in Enugu, Nigeria (6.0%) in 2010, Adegoke *et al* [23] in Lagos, Nigeria (6.6%) in 2013 and Yauba *et al*[24] in Zaria, Nigeria (2.2%) in 2014. There are some similarities in the study design and methodology used in the previous studies compared to the extant regarding age group stratification and use of repeated urine samples in the confirmation of ASB. However, the higher prevalence rate in the current study could be a true reflection of the effects of conditions in the study locale that predispose to ASB (the peculiar environmental factors of high altitude, moderate rainfall, low temperature, and low humidity which are known triggers of recurrent hypoxaemia and sickling that can lead to papillary necrosis and hyposthenuria).[14, 15]

This study also observed a higher prevalence of ASB in SCA patients compared to that reported by Ocheke *et al* [18] in 2016 in Jos, who found prevalence rate of 4.3% in HbAA children, thus supporting the fact that individuals with SCA have increased predilection to ASB/UTI compared to their Hb AA counterparts despite that the study by Ocheke *et al* [18] utilised single urine sample for the establishment of the presence of ASB.

The prevalence figure in the present study is markedly lower than the previous ones as reported by Asinobi *et al* [25] in Ibadan, South-west Nigeria (21.0%) in 2004 and Mava *et al* [26] in Maiduguri, North-east Nigeria (26.0%) in 2011. The lower value in the current study compared to others may be explained by the fact that subjects in the extant study were asymptomatic compared to what obtained in the previous studies where subjects were symptomatic. Furthermore, the higher prevalence observed in the Maiduguri study may be a reflection of the high environmental temperature which is a risk factor for dehydration leading to sickling, stasis of urine and increased incidence of UTI and renal stones.

The prevalence of ASB in age and gender matched controls was 1.5% and this is comparable to that reported by Chukwu *et al* [22] (2.0%) and Abdulrahaman *et al* [27] (1.0%). Conversely, a higher value (20.0%) was reported by Mava *et al* [26] in Maiduguri, Nigeria among children aged 6months – 15 years. Unlike in Mava*'s* study,[26] young infants were not included in the current study, and this could explain the lower prevalence rate obtained.

The low prevalence of ASB in controls compared to subjects as observed in this study further re-affirms the assertion that the burden of ASB in children with SCA compared to those without SCA is higher. Perhaps even higher prevalence figures may have been obtained in subjects compared to controls if individuals in crises rather than steady state were recruited or if subjects with other forms of SCD were included. There is therefore a need for early detection of ASB through regular/routine screening. There is also a need to institute measures to halt its progression before it leads to more established renal conditions.

In this study, the prevalence of ASB was significantly higher among female SCA patients (15.2%) compared with their healthy male counterparts (3.0%), with a female to male ratio of 10:1 for the SCA group, which is comparable to the findings by Ajasin *et al* [8] who also reported a female to male ratio of 10:1.This observation is in tandem with reports contained in several literatures that observed female preponderance of varying ratios. [12, 17, 25-28]

The factors suggested to explain this variation include short female urethra and its proximity to the anal orifice which makes it easier for migration of gut flora to the urinary tract and the relative deficiency of secretory IgA antibody response from the mucosal surface in the female urinary tract which makes the female gender more at risk for UTI.[28]

This study noted that ASB was more common in pre-school subjects and least in the adolescents. The prevalence of ASB therefore declined with increasing age. A similar trend was also noted by Yauba *et al*. [24] This may be explained by the fact that children below the age of 5 years are still undergoing toilet training which is a risk factor for UTI.[29]

In contradiction, Chukwu *et al* [22] found a higher prevalence of ASB in children older than five years of age; an observation they attributed to higher risk of sexual abuse and delayed voiding of urine with subsequent retention. These factors favour bacteria growth in the older children.

Several authors [24,28] had previously documented the strong association between social class and prevalence of ASB with predilection for individuals from lower socioeconomic class. In contrast to such observation this study noted that a higher proportion of children with ASB were from the upper social class. This is consistent with the findings by Chukwu *et al*[22] who found significantly higher prevalence of ASB in subjects drawn from upper social class.

The trend could be a reflection of practices where children in upper social class engage in activities with prolonged screen time (including computer games, TV, social media) causing delayed voiding and attendant retention of urine which are known risk factors for ASB. One limitation of this study is that only children with SCA (HbSS) and those in steady state were recruited as subjects. This may have caused an underestimation of the true burden of the disease as those with other forms of the haemoglobinopathy and those in crises were excluded.

CONCLUSION

This study found a high prevalence of asymptomatic bacteriuria in children with sickle cell anaemia and this was higher than the prevalence rate among their age and sex-matched HbAA counterparts. Girls with sickle cell anaemia are more predisposed to asymptomatic bacteriuria than boys.

We recommend routine screening of children with SCA for ASB. This will help to detect cases of ASB early, such that intervention could then be instituted to forestall disease progression, thereby reducing childhood morbidity and mortality.

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Disclosure

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Conflicts of interest

There are no conflicts of interest.

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