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Pulmonary Hypertension in Adults with Sickle Cell Anaemia: A Prevalence Study in the Niger Delta Region of Nigeria

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Authors' contributions

This work was carried out in collaboration between both authors. Author ANM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors ANM and CAA managed the analyses of the study. Authors ANM and CAA managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Introduction: Sickle cell anaemia (SCA) is a lifelong multisystem disease endemic in sub Saharan Africa. As the population of patients living with SCA into adulthood continues to increase, pulmonary hypertension has emerged as one of the foremost complications with severe implications on the quality of life and a risk factor for premature mortality.
Aims: The present investigation is a prevalence study in the Niger Delta region regarding pulmonary hypertension in adults with sickle cell anaemia.
Methods: One hundred and six adults were recruite; fifty-three sickle cell anaemia patients recruited from the outpatient clinic of the haematology department of the University of Port Harcourt teaching hospital, Port Harcourt and 53 genotype AA adults recruited as control. Transthoracic echocardiography was performed on all 106 subjects. The prevalence of pulmonary hypertension was assessed based on tricuspid regurgitation jet of velocity ≥2.5 m/s (estimated SPAP≥30 mmHg).

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Results: The mean age of the SCA patients was 25.94±6.47 years, (range 18-45 years) while the age group with the highest representation was those within 18–27 years. The proportion of males (52.8%) was slightly higher than that of the females. Pulmonary hypertension was observed in 5.7% while high normal pulmonary artery pressure was observed in 1.9% of the SCA patients studied.
Conclusion: The prevalence of pulmonary hypertension in adults living with Sickle Cell Anaemia in this study is 5.7% and it is significantly influenced by the age of the study cohort and the method used in assessing this parameter.

Keywords: Pulmonary hypertension; adults; sickle cell anaemia; prevalence; Niger Delta region.

1. INTRODUCTION

Sickle Cell Anaemia (SCA) which is the commonest haemoglobinopathy worldwide having the highest prevalence documented in sub-Saharan Africa (over 12 million cases reported) has been identified as the most common and severe monogenic disease [1-2].

In Nigeria, the prevalence of SCA is reported as 2–3 per cent of the population [3-4]. One to 15% of patients in Nigeria are diagnosed in the first decade of life, with a death rate of 5% in the subsequent decade [4].

Fifty per cent of these patients are expected to survive beyond 50 years of age 6 as, during the last twenty years, the treatment modalities for SCA have remarkably improved with consequent higher survival rates [5]. As life expectancy continues to improve with early diagnosis, better care and treatment of this disease, there is a growing concern as more chronic complications of this disease emerge. Among the foremost of these complications is secondary pulmonary hypertension, a vascular complication of several diseases, now increasingly reported in adults with sickle cell disease [5].

Pulmonary hypertension which is increasingly recognized in patients SCA, with the prevalence reported as high as 30% in echocardiography-based studies [6-7] has also been documented over the last several decades as an important, progressive disease with significant impact on the quality of life of its sufferers in addition to high mortality outcomes, irrespective of the class of its primary cause [4]. Pulmonary hypertension (PHT) is defined as elevated mean pulmonary artery pressures measured during right-sided cardiac catheterization [8-11]. Non-invasive Echocardiography evaluation of the Tricuspid Regurgitant Velocity (TRV) remains a very vital screening instrument for PHT determination [12-13]. TRV estimates the pulmonary artery systolic pressure using the Bernoulli equation (Pulmonary Artery Systolic Pressure = 4 $(TRV)^2$ + Right Atrial Pressure) [12]. In SCD, this estimated pulmonary systolic pressure is documented to fairly correlate with measurements obtained by cardiac catheterization [6]. A value of 2.5 m /s or more corresponds to an estimated pulmonary artery systolic pressure of 35 mm Hg [14].

SCA is associated with reduced life expectancy and early death, and pulmonary hypertension (PH) is reported to play a significant role in this regard [1-2] as PH is a well-documented severe and life-threatening complication of SCA associated with accelerated mortality [6,15]. PH which may be described as a clinically silent disease until the late stage is reported in 20% to 40% of adults with high mortality of 40% or 10-fold higher compared with those with normal TRV [6,16].

Pulmonary hypertension is an established complication of the haemolytic anaemias via the common pathway of hemolysis, causing endothelial dysfunction and oxidative/ inflammatory stress, chronic hypoxemia, chronic thromboembolism, chronic liver disease, iron overload and asplenia [5].

In Nigeria, especially in the Niger Delta region, there are limited studies on PH in SCA. Hence this study which was aimed at the determination of the prevalence of Echocardiography-derived PH will contribute to the data bank on PH in SCA in Nigeria, Africa and globally thereby contributing to the identification and management of this condition which is a public health concern [3].

2. METHODS

The study is a cross-sectional, descriptive and comparative study involving 106 adults with an age range of 18 to 65 years in the Niger Delta Region of Nigeria. Fifty-three homozygous haemoglobin S (HbSS) adults who gave

informed consent and in steady-state were consecutively recruited from the Sickle Cell Anaemia out-patient clinic of the Department of Haematology at the University Of Port Harcourt Teaching Hospital. Diagnosis of SCA (HbSS) had been confirmed previously by haemoglobin electrophoresis. Steady-state was defined as a crisis-free period of at least 3 weeks, with at least 3 months since the last blood transfusion. A comparison group included fifty-three healthy, HbAA adults who also gave informed consent and were recruited as control.

The University of Port Harcourt Teaching Hospital (UPTH) serves as a referral Centre for Rivers State and most of the neighbouring states which include, Bayelsa, Abia, Akwa-Ibom and Imo states of Nigeria.

Demographic information and baseline biometric values were obtained.

Transthoracic echocardiography using Mindray DC–N6® diagnostic ultrasound imaging system was performed on all the recruited subjects. Two dimensional and motion mode (M mode) guided and doppler measurements were obtained. Calculations were made using the cardiac analysis software of the echocardiographic machine. Tricuspid regurgitation jet was assessed in the parasternal right ventricular inflow, parasternal short axis and apical four-chamber views to determine the highest velocity. Continuous-wave Doppler sampling of the peak regurgitant jet velocity was used to estimate the right ventricular to right atrial systolic pressure gradient. The Bernoulli equation was used to calculate the pulmonary artery systolic pressure (SPAP), with mean right atrial pressure estimated according to the degree of inferior vena cava collapse with inspiration. Tricuspid regurgitation jet velocity ≥2.5 m/s (estimated PAP≥30 mmHg) was considered pulmonary hypertension [5-6].

Data were analyzed using SPSS version 20.0 statistical package. Results were presented as mean, standard deviation and percentages. Continuous variables were compared by the independent student's t-test. Proportion or categorical variables were analyzed with the Chi-square test or two-tailed Fischer's exact test as appropriate. P– Values of less than 0.05 were considered statistically significant.

3. RESULTS

The mean age of the subjects was 25.94 ± 6.47 years, (range 18-45 years) while the age group with the highest representation was those within 18–27 years. The proportion of males (52.8%) was slightly higher than that of the females (47.2%) giving a male to female ratio of 1.1:1, and the entire study population was Nigerian. The largest ethnic group represented was Ikwerre, followed by the Igbo, 17%, Kalabari ethnicity constituted 15% and Ijaw 13%. Other ethnic groups constituted <4% of the total population.

The clinical characteristics of the study group are reflected in Table 1.

Pulmonary pressure was estimated using peak tricuspid regurgitant jet velocity and right atrial pressure estimated from the degree of inferior vena cava collapsibility. Subjects with no detectable tricuspid regurgitation were documented as having normal pulmonary pressure, (SPAP). Of those who had detectable tricuspid regurgitation, those with tricuspid regurgitation jet velocity ≥2.5 m/s (estimated PAP≥30 mmHg) were documented as pulmonary hypertension and further categorized as shown in Table 2. Pulmonary hypertension was observed in 5.7% while high normal pulmonary artery pressure was observed in 1.9% of the SCA patients.

Table 1. Clinical characteristics of SCA patients and control

Variable	Subjects N=53 Mean±SD	Control N=53 Mean±SD	P-Value
Weight(Kg)	59.496±10.384	63.979±7.9205	0.01**
Height(cm)	167.3±8.596	165.9±10.939	0.464
BMI(Kg/m2)	21.2±2.972	23.6±3.789	0.01**
Heart Rate(Bpm)	76.83±11.537	70.85±8.893	0.01**
Systolic BP(mmHg)	112.26±11.205	113.83±10.7836	0.465
Diastolic BP(mmHg)	69.66±8.428	72.51±7.836	0.07
BSA	1.665±0.167	1.709±0.138	0.01**

*Significant level <0.05 *, <0.01**; BP, Blood Pressure, BSA, Body surface area, BMI, Body mass index, Bpm, Beats per minute*

Table 2. Prevalence of pulmonary hypertension in SCA patients by tricuspid regurgitation jet velocity

PAP(mmHg)	N	%
Normal (18-25)	49	92.45
High Normal (26-29)	1	1.88
Mild (30-40)	3	5.66
Moderate (41-70)	0	0
Severe (>70)	0	0
Total	53	100.0

Table 3. Right atrial volume, right atrial volume index and right ventricular free wall thickness

Variable	Subjects N=53 Mean±SD	Control N=53 Mean±SD	P-Value
RAV(ml)	62.15±15.80	51.939±10.54	0.001**
RAVI(ml/m^2)	37.65±10.01	31.15±4.96	0.001**
RVWT(cm)	0.61±0.13	0.52±0.50	0.001**

*Significant level <0.05 *, < 0.01**, RAV, right atrial volume; RAVI, right atrial volume index; RVWT, right ventricular wall thickness*

The right atrial volume, right atrial volume index and right ventricular free wall thickness were also measured and these indices were found to be significantly higher in the SCA patients compared to the controls (p=0.001).

The right ventricular free wall thickness was measured in the subcostal view with 2D in end-diastole for both SCA patients and controls. See Table 3.

4. DISCUSSION

The pulmonary vascular system is typically a low-pressure system, unfortunately, it is the system that receives the highest amount of injuries in sickle cell anaemia [1]. This is further compounded in sickle cell anaemia patients living in sub-Saharan Africa, where, community-acquired respiratory infections aside, there is increased risk of contact with other conditions known to have a propensity for pulmonary vasculopathy, foremost being HIV infection, others include schistosomiasis.

Pulmonary hypertension (PH), has now emerged as the foremost risk factor for morbidity and premature mortality in sickle cell anaemia [1-5, 17-18]. The pathophysiology of pulmonary hypertension in sickle cell anaemia is multifactorial and not completely understood, hence the classification in class 5.1 of the updated classification of pulmonary hypertension made at the fifth world symposium on PH in Nice, Italy, 2013 [4]. It is a fact that PH is a severe complication of SCA with implications on the quality of life of the patient and a very real risk of premature mortality. The relationship between pulmonary hypertension and outcomes in SCA has been documented in literature including randomized multicenter studies by Parent and others [19]. These studies reveal the need for screening for PH in SCA [1-5,17-18,20]. As in other diseases, for screening tests to be beneficial, early identification of the disease should be beneficial and treatment available to cure or at least slow down the progression of the disease. In planning for screening for any disease knowledge of the prevalence of the disease is pertinent. Aliyu, et al. found pulmonary hypertension in 25% of the 178 sickle cell anaemia patients studied at Zaria, Nigeria [18]. Oguanobi, et al. in their study at Enugu, Nigeria, found mildly raised pulmonary pressures in 78% and pulmonary hypertension in 38% of SCA patients studied [21]. A prevalence of 41.9% of the 62 SCA patients evaluated was reported two years later [22]. Meanwhile, Ike, et al. also at Enugu, Nigeria, had earlier, reported pulmonary hypertension in only 3 of 56 patient (5%), assessed [23]. This disparity is likely due to the difference in methodology of assessing pulmonary artery pressure. Echocardiographic estimation of pulmonary artery flow acceleration time was used to derive the mean pulmonary artery pressures in the later study while tricuspid regurgitant flow velocity was used in the earlier study [22-23].

Dosunmu, et al. in Lagos, south-west Nigeria, in their study of 56 patients age 14–42 reported pulmonary hypertension in 3.6% of the 56 patients studied [24]. The low prevalence demonstrated in the study was ascribed to the younger age of the study population [25]. Enakpene, et al. at Ibadan reported a prevalence

of 12.2% using the tricuspid regurgitant jet velocity of ≥2.5 m/s [26]. The mean age of that cohort was reported as 24 years, however, the cohort included SCA patients in frank heart failure. These studies also reported a correlation between pulmonary hypertension and advancing age in patients with sickle cell anaemia in Nigeria [18,22-24,26]. A recent systematic review by Caughey et al using random-effects meta-analysis of a total of 45 studies representing 15 countries and 6109 individuals using estimated pulmonary artery pressure (ePAP), defined by a tricuspid regurgitant velocity of 2.5 m/s, reported a prevalence of 30% in adults with SCA [27]. Parent and others reported a prevalence of 27% based on tricuspid regurgitant jet velocity (TRV) of ≥2.5 m/s with confirmation using right heart catheterization [19]. The correlation of identifying elevated systolic pulmonary artery pressure using Doppler echocardiography and right heart catheterization was found to be moderate, improving by increasing the cut off of TRV from 2.5 to 2.9 m/s, however, the investigators observed that a significant number of patients with elevated pulmonary artery pressures would be missed if the cut off is increased. The study further buttressed the relevance of Doppler echocardiography as a screening and diagnostic tool in pulmonary hypertension.

5. CONCLUSION

The prevalence of pulmonary hypertension in adults living with Sickle Cell Anaemia in this study is 5.7% and it is significantly influenced by the age of the study cohort and the method used in assessing this parameter.

CONSENT

As per international standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard, written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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