



PREVALENCE AND PATTERN OF RESPIRATORY SYMPTOMS IN ADULTS WITH SICKLE CELL DISEASE: A CROSS-SECTIONAL ANALYSIS

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ABSTRACT

Background: Sickle cell disease is one of the common genetic diseases worldwide. The highest prevalence of this disorder occurs in the middle East, Mediterranean region, South East Asia and sub-Saharan Africa especially Nigeria. The study is aimed at assessing the common respiratory symptoms (e.g., cough, wheezing, chest tightness, dyspnea) in adult SCD patients at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi.

Method: This is a cross-sectional case-control study carried out over a period of one (1) involving adult SCD patients attending the Out-patient Sickle cell Clinic at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, South-Eastern Nigeria. Data were analyzed using Statistical Package for Social Sciences (SPSS version 21.0).

Result: The study compared 50 adult SCD patients in a steady state to 50 healthy controls. The age range (AR) of the patients was 18-35 years with a mean age of 24.20 ± 2.53 years. SCD patients showed significantly higher rates of respiratory symptoms. 36.0% of the study participants developed cough only with infection while 20.0% did not develop cough at all. 56% SCD patients produced sputum only with infection in the past four weeks while only 8% subjects produced sputum a few days in a month. 38% of the control group produced sputum only with infection and none it a few days in a month ($p=0.02$). 56.0% of SCD patients had shortness of breath only with infection whereas none of the control group experienced shortness of breath at any time in the previous four weeks. 16.0% of study subjects experienced it almost every day. ($p=0.01$)

Conclusion: Sickle cell disease patients frequently experience shortness of breath and sputum production. Routine screening and early interventions are crucial to slow lung function decline. More research is needed to pinpoint respiratory symptoms and risk factors, evaluate intervention effectiveness, and understand the diagnostic value of pulmonary function testing to improve early detection and management.

KEYWORDS: prevalence, respiratory symptoms, adults, sickle cell disease.

INTRODUCTION

Sickle cell disease is one of the common genetic diseases worldwide. The highest prevalence of this disorder occurs in the middle East, Mediterranean region, South East Asia and sub-Saharan Africa especially Nigeria.(1,2) About 50 million people worldwide live with Sickle Cell Disease (SCD), and Nigeria is at the heart of this global health challenge. (3) About 5-7% of the global population

carries an abnormal haemoglobin gene and 70% of all affected birth occur in Africa.

Nigeria, Africa's most populous country with a population of 206 million, is probably the country with the world's largest population of individuals with sickle cell disease.(4) With approximately 4 to 6 million Nigerians affected, the country bears a significant burden of the disease. This means that roughly one in every four Nigerians carries the sickle cell trait. (3) The prevalence

of Sickle Cell Disease (SCD) across different states in Nigeria typically falls within a range of 1% to 3%. The most common type of SCD found in Nigeria is Hb-SS, while Hb-SC occurs less frequently, particularly in the southwestern region of the country. (5,6) Lung involvement accounts for mortality rate of more than 20% in sickle cell anaemia patients and is also a key determinant of their survival.(7,8) Clinical pulmonary involvement in the sickle cell patient commonly takes two forms: Acute chest syndrome (ACS) and Sickle cell chronic lung disease (SCCLD).(8,9)

Sickle Cell Disease (SCD) can manifest in diverse ways, with patients presenting a range of clinical issues. These can include leg ulcers, priapism, persistent fatigue, dizziness, osteonecrosis (bone death), bloodstream infections (bacteraemia), and dactylitis (swelling of hands and feet). More severe complications may involve kidney disease, pulmonary hypertension (high blood pressure in the lungs), acute chest syndrome, and damage to various organs.(10)

SCD is one of the most common genetic blood disorders and the greatest burden of lies in Sub-Saharan Africa and Asia.(11) The prevalence of sickle cell trait ranges between 10% and 45% in various parts of Sub-Saharan Africa while in Nigeria, carrier prevalence is about 20-30%. (12,13) SCD affects about 2-3% of the population in Nigeria (14) with the prevalence in Benin city, Southern Nigeria estimated to be about 11%. (6)

The carrier rate of sickle cell trait in Nigeria is as high as 26.94% (15)and the prevalence rate of sickle cell disease in Nigeria is estimated at 3.54%.(16) The mean age at death is 21years and of those who survive, there is significant morbidity involving various organs including the lungs.(17) Sickle cell disease, therefore, imposes a lot of socioeconomic burden on the sufferers and care-givers.(18) In spite of this burden there is a paucity of data, especially in South-Eastern Nigeria.

The study aimed at assessing the common respiratory symptoms (e.g., cough, wheezing, chest tightness, shortness of breath (dyspnea)) in adult SCD patients at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi.

MATERIALS AND METHODS

Study Design

This was a cross-sectional case-control study carried out over a period of one (1) year(from January 1st to 30th December 2018) involving consenting adult sickle cell disease patients attending the Out-patient Sickle cell Clinic at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, South-Eastern Nigeria.

This study was carried out at the Haematology clinic of the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State.

The study population consisted of adult sickle cell patients aged 18 – 35years (predominant age group as recorded in the sickle cell register), in stable state, attending the Haematology outpatient clinic of the NAUTH, Nnewi, whose HbSS was already confirmed by haemoglobin electrophoresis, and who met the inclusion criteria. Participants in the control group were healthy adults with Haemoglobin AA(HbAA) genotype selected among medical students matched for sex and age. All participants gave a written informed consent

Sample Selection

The study participants who had been attending the sickle cell clinic in the past one year were recruited consecutively.

Participants in the control group were selected from among medical students of the NAUTH who gave their consent and further underwent haemoglobin electrophoresis. Only students with HbAA genotype were selected to form part of the sampling frame.

Sample Collection

Demographic characteristics were documented. Clinical history was obtained from the patients and examinations carried out. Past medical history, history to rule out acute or chronic respiratory conditions and advanced heart failure and any sickle cell complication developed in the past one year were obtained from study participants. Anthropometry (weight, height and body mass index), lung function and oxygen saturation were measured in study participants and documented.

A semi-structured study proforma using the modified St. Georges Respiratory Questionnaire (SGRQ)(19,20) was investigator-administered (Appendix 4). It captured participants demographic characteristics, respiratory symptoms, allergies, environmental factors, history of cigarette smoking, other co-morbidities, current

medications and assessment of disease severity using objective sickle cell severity score (Hedo et al).(21)

Weight was measured in kilograms using Avery scales (Avery Berkel, 2003, UK). The subjects were made to remove their shoes and any piece of items or objects in their possession that may have added to their weight. The subjects were asked to mount the scale and the weight read off in kilograms.

Standing height was measured in centimeter using a wall mounted stadiometer.

Participants were asked to remove shoes, heavy outer garments, and hair ornaments.

Participants were asked to stand with his/her back to the height rule. The back of the head, back, buttock, calves and heels were touching the upright rule, feet together. The top of the external auditory meatus was levelled with the inferior margin of the bony orbit. The participant was asked to look straight ahead.

The head piece of the stadiometer or the sliding part of the measuring rod was lowered so that the hair (if present) was pressed flat.

Height was recorded to the resolution of the rule. If the participant was taller than the measurer, the measurer stood on a platform so that he/she could properly read height rule.

For participants that were excluded from height measurement, the reasons were noted.

The weight and height of each subject was used to determine the individual's Body-Mass Index (BMI) using the formula:(22) $BMI = \text{Weight (in kg)} / \text{square of the height (in meters)}$.

BMI was categorized into: **Underweight:** <18.5; **Normal weight:** 18.5-24.9; **Pre-obesity:**25.0-29.9;**Obesity class I:**30-34.9;**Obesity class II:**35.0-39.9 and **Obesity class III:**≥40

Subjects sat on a chair with the back supported and the right arms bared and supported at heart level and over inflation was avoided by estimating the maximum inflation point through palpating the radial pulse while incrementally inflating the balloon of an Accoson mercury sphygmomanometer until the pulse disappeared as to avoid inducing sickle cell crisis. Blood pressure measurement was performed on each subject after five minutes of rest with the cuff of the mercury sphygmomanometer applied on the right arm of the subject. First and fourth Korotkoff sounds were recorded for systolic and diastolic readings, respectively.

Diagnosis of Sickle Cell Disease

Diagnosis of sickle cell anaemia was based on clinical and haematological findings of sickle cell as well as haemoglobin (Hb) electrophoresis (using cellulose acetate strip) on venous blood samples collected from the patients as described by the International Committee for Standardization in Haematology.¹⁰³ The controls were non-sickle cell disease subjects with HbAA (electrophoresis carried out as for the sickle cell anaemia patients).

Data Analysis

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS version 21.0). Results were presented as mean + standard deviation (SD) for continuous variables while categorical variables were expressed as proportions or percentages. Continuous variables were compared using the student's t-test, while proportions or categorical parameters were compared with the chi-square test or two-tailed Fisher's exact test as appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

One hundred (100) participants were studied comprising 50 adult sickle cell disease (SCD) patients in steady state (subjects) and 50 normal adults (control).

TABLE 1- Age and Sex Distribution of the Study Participants

Age categories (in years)	Subject(n=50)			P Value	Control(n=50)			P Value
	M(%)	F(%)	TOTAL		M(%)	F(%)	TOTAL	
≤20	1(3.57)	1(4.54)	2(100)	0.321	2(6.67%)	2(10.0)	4(100)	0.423
21-25	12(42.86)	13(59.09)	25(100)		18(60.0)	14(70.0)	32(100)	
26-30	13(46.43)	7(31.81)	20(100)		9(36.0)	4(20.0)	13(100)	
31-35	2(10.71)	1(4.54)	3(100)		1(3.33)	-	1(100)	

Age/Sex Distribution

The age range (AR) of the patients was 18-35 years with a mean age of 24.20(2.53) years. That of the control was 18-35 years with a mean of 22.56(2.2) years. The age range (AR) of male and female study subjects were 20-35 and 18-33 respectively while the age range of male and female control subjects were 18-35 and 19-32 respectively. There were 28 (56.0%) males and 22 (44.0%) females in the patient group; while the control group had 30 (60.0% of control group) males and 20 (40.0%) females. The mean ages of male and female

sickle cell anaemia subjects were 23.6(2.1) and 24.6(2.4) years respectively ($p=0.903$). The mean ages of the male and female control subjects were 21.8 (2.1) and 23.32(2.2) years respectively ($p=0.912$). The ages in both groups were therefore similar being a case-controlled study. These are as shown in table 1. The difference in ages was not statistically significant ($p=0.423$). Hence, a male to female ratio of 1:1.3 and 1:1.5 for sickle cell disease and control populations respectively. The sex difference between these populations was not statistically significant ($p=0.231$).

TABLE 2- Demographic/Anthropometric Characteristics of the Study Participants

Patients characteristics	Subjects(n=50)	Controls(n=50)	P value
Igbo	41(82.0%)	44(88.0%)	0.941
Yoruba	4(8.0%)	2(4.0%)	
Ibibio	3(6.0%)	1(2.0%)	
Efik	(0.0%)	1(2.0%)	
Hausa	2(4.0%)	2(4.0%)	
Sex of participants			
Male	28(56.0%)	30(60.0%)	0.231
Female	22(44.0%)	20(40.0%)	
Mean age(SD) years	24.20(2.53)	22.56(2.2)	0.817
Mean height (SD) in cm	172.88 (6.26)	172.86(6.1)	0.946
Mean weight (SD) in kg	66.00 (8.42)	64.64 (7.97)	0.411
Mean BMI (SD) in kg/m ²	21.70 (3.07)	22.07 (2.32)	0.509

Demographic/Anthropometric Characteristics of the Study Participants

The heights of the study and control groups were 172.88(6.25) cm and 172.86(6.5)cm respectively ($p=0.946$). The mean heights for the male study subjects and male controls were 178.22(6.7) cm and 176.26(6.8) cm respectively ($p=0.945$), and the mean heights for the

female subjects and controls were 167.5 (5.8) cm and 169.5(6.0) cm respectively ($p=0.812$).

Mean weights of the study and control participants were 66.0(8.42) kg and 64.64(7.97) kg respectively. The difference was not statistically significant ($p=0.411$). The mean weights for the male study subjects and male controls were 67.3(3.2) kg and 67.6(3.1) kg respectively ($p=0.213$) while the mean weights for the female study

subjects and female controls were 61.5(2.2) kg and 64.4(2.5) kg respectively ($p=0.211$).

The study group had a mean BMI of 21.20(3.07) kg/m² while that of the control group was

22.07(2.32) kg/m². The mean BMI values did not differ significantly from each other ($p= 0.509$). The mean BMIs

for the male study subjects and male controls were 22.54 (2.3) kg/m² and 22.3 (2.12) kg/m² respectively($p=0.201$) while the mean BMIs for the female study subjects and female controls were 21.6 (2.14) kg/m² and 20.1(2.01) kg/m² respectively ($p=0.202$).

TABLE 3- PATTERN OF RESPIRATORY SYMPTOMS

RESPIRATORY SYMPTOMS	PATTERN OF SYMPTOMS	Subjects (n=50)	Controls (n=50)	p-value
COUGH	Not at all	10(20.0%)	31(62.0%)	0.03
	Only with infections	18(36.0%)	19(38.0%)	
	A few days a month	3(6.0%)	0(0.0%)	
	Several days a week	9(18.0%)	0(0.0%)	
	Almost everyday	10(20.0%)	0(0.0%)	
Phlegm in the last 4 weeks	Not at all	0(0.0%)	31(38.0%)	0.02
	Only with infections	28 (56.0%)	19(38.0%)	
	A few days a month	4(8.0%)	0(0.0%)	
	Several days a week	8(16.0%)	0(0.0%)	
	Almost everyday	10(20.0%)	0(0.0%)	
SOB in the last 4 weeks	Not at all	0(0.0%)	50(100.0%)	0.01
	Only with infections	28(56.0%)	0(0.0%)	
	A few days a month	4(8.0%)	0(0.0%)	
	Several days a week	10(20.0%)	0(0.0%)	
	Almost everyday	8(16.0%)	0(0.0%)	
Wheezing in the last 4 weeks	Not at all	18(36.0%)	50(100.0%)	0.02
	Only with infections	10(20.0%)	0(0.0%)	
	A few days a month	6(12.0%)	0(0.0%)	
	Several days a week	8(16.0%)	0(0.0%)	
	Almost everyday	8(16.0%)	0(0.0%)	

Common Respiratory Symptoms

Respiratory symptoms were commoner in sickle cell disease (anaemia) compared with the control(normal)subjects. Eighteen (36.0%) of the study participants developed cough only with infection while 10(20.0%) did not develop cough at all. In the control population, 19 (38.0%) developed cough only with infection while 31(62.0%) did not develop cough at all ($p=0.03$) as seen in table 3 above.

28 (56.0%) sickle cell patients admitted to producing sputum only with infection in the past four weeks while only 4(8.0%) subjects produced sputum a few days in a month. Nineteen (38.0%) persons in the control population produced sputum only with infection and none produced sputum a few days in a month. ($p=0.02$)

Twenty-eight (56.0%) sickle cell patients had shortness of breath only with infection whereas none of the control subjects had shortness of breath at any time in the

previous four weeks. Eight (16.0%) study subjects developed shortness of breath almost every day. ($p=0.01$)

Ten (20.0%) of the study subjects wheezed only with infection as against none of the control subjects wheezing only with infection. Only 8 subjects (16.0%) of the sickle cell population wheezed almost every day in contrast to the control population in which none wheezed daily. ($p=0.02$)

DISCUSSION

The age range of the subjects was 18-35yrs, and is similar to that in other studies. The reason for poor representation of the older person may be due to high mortality rate of SCD or early death due to poor health care seeking behavior of the population or absence of health care service. Some also might have receive alternative medicine or not at all. The similarity in anthropometric parameters of the subject/control population could suggest the good quality of health care service to the subjects from the tertiary center. The average body weight and BMI of Hb-SS subjects in this study was comparable to that of the Hb-SS subjects in studies done by Ozoh et al(8) and Klings et al.(23) This could be because patients are in a stable state and access standard medical care in a teaching hospital where the study was carried out .

The common respiratory symptoms found were shortness of breath (SOB) and sputum production accounting for 56.0% each. This is similar to that reported by Fawibe et al(24) where shortness of breath was seen in 58.8% of the study subjects. Also, Ozoh et al(8) reported SOB to be 52% in SCD patients with males 18.9% and females 23.6%. Their finding on sputum (phlegm) production was 10% which is lower than what was found in this study. Fawibe et al posited that the presence of symptoms could be due to acute chest syndrome. The reason for the relatively high frequency of shortness of breath and sputum production could be due to high prevalence of chest infection in persons with this condition. Vichinsky et al(25) in their study noted that more than two thirds of SCD patients had a history of the chest infection, and many had multiple episodes during the study. SCD is associated with immune depression with defective opsonization. Jain et al(26) in their study, concluded that there is a significant relationship between abnormality of ventilatory function and previous symptoms associated with acute chest syndrome. There is an increased awareness that acute chest syndrome accompanied by fever, chest pain, tachypnea, wheezing, or cough, is the

leading cause of death in a patient with SCD.(27) Fonseca et al(28) however reported the most common respiratory symptom to be cough, seen in 63% of the study population. The difference between this study and theirs may be due to the modalities of obtaining the required information. In this study, the St Georges respiratory Questionnaire was used while they interviewed the patient guardians, apparently the patients were children. Howard et al(29) observed that the commonest respiratory symptom in their study was cough, more common in winter season but stated that the clinical symptoms can vary depending on age. Young children more often present with cough and wheeze whereas chest pain and shortness of breath are predominant features in adult. The least common respiratory symptom in adults was wheezing and reason could be that most patient do not consider wheeze as a significant symptom.

The least respiratory symptom in this study was cough which is similar to the work done by Ozoh et al(8) and Fawibe et al.(24) The reason for this is not really known but patients trivializing cough because of its chronicity and possibly the frequent use of cough suppressant during episodes or view cough as a normal event.

CONCLUSION

Sickle cell disease patients in this study commonly reported shortness of breath and sputum production. Given the significant burden of pulmonary dysfunction, routine screening and timely interventions are important to slow lung function decline. Further research is needed to identify respiratory symptoms and risk factors and assess the effectiveness of potential interventions, ultimately informing strategies for early detection and management. A deeper understanding of pulmonary function testing's diagnostic value in this population could provide valuable insights into the causes of shortness of breath and sputum production.

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