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Pulmonary functions in children with sickle cell anaemia in steady state in Lagos, Nigeria

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Abstract

Background: Respiratory disorders are responsible for considerable morbidity and mortality in children with sickle cell anaemia (SCA). Spirometry is a useful tool for the detection and monitoring of respiratory disorders, but it is under-utilized by healthcare workers who care for children with sickle cell anaemia. Most of the studies assessing pulmonary functions in sickle cell anaemia were conducted among adults.
Objective: To describe the lung functions profile of children with sickle cell anaemia in steady state.
Methodology: In this study, spirometric indices of 100 children with SCA (HbSS) aged five years to 12 years were compared with 100 matched normal children (HbAA) in the control group.
Results: Irrespective of gender, the mean Peak Expiratory Flow Rate (PEFR) values were significantly higher among the HbAA controls than their HbSS counterparts. The mean Forced Expiratory Volume in one second **(**FEV_1) values of males and all subjects irrespective of gender were also significantly higher among the controls compared to HbSS subjects. The mean Forced Vital Capacity (FVC) values were higher among HbSS subjects than the HbAA controls, but the observed differences were not significant. The mean FEV_1/FVC values were also not significantly different between the SCA subjects and the controls. The overall prevalence of restrictive pulmonary abnormalities among the HbSS group was 6.0% whereas none of the HbAA group had restrictive pulmonary disorders.
Conclusion: Children with SCA, irrespective of gender, have significantly lower PEFR and FEV_1. Restrictive lung abnormalities occur exclusively among subjects with SCA.

Keywords: Obstructive Lung Diseases; Peak Expiratory Flow Rate; Restrictive Lung Disease; Sickle Cell Anaemia; Spirometry.

Introduction

Sickle cell disease is one of the leading genetic disorders worldwide, and it is the most common inherited haematological disease affecting man. [1] This condition is inherited as an autosomal recessive disorder. The homozygous state, otherwise

known as sickle cell anaemia (SCA), is a lifelong disorder affecting about 2-3% of newborns. [2] This disease is associated with remarkable morbidities and mortality, and this makes it a major health problem in Nigeria. With the population of Nigeria at about 140 million and of which about 50% are children, [3] it is estimated that about 4.2 million Nigerians are suffering from sickle cell anaemia.

The sickling phenomenon is the primary pathogenesis in SCA; this is characterised by obstruction of the microvasculature by abnormally shaped (sickled) red blood cells. This phenomenon affects all organs and tissues of the body including the lungs. [4] The recurrence of sickling may lead to deterioration of lung functions as a result of potential complications such as lung fibrosis, chronic hypoxia and pulmonary hypertension. [5] SCA presents with pulmonary complications such as the acute chest syndrome, pulmonary thromboembolism, pulmonary fat embolism and lung fibrosis. These abnormalities also referred to as sickle cell chronic lung diseases (SCCLD), are often heralded by recurrent acute chest syndrome in late infancy and early childhood. It is progressive in nature and continues into adulthood causing pulmonary hypertension, heart diseases and death. [6, 7] Lung functions abnormalities in SCA can be obstructive, restrictive or both. The exact prevalence of SCCLD and the methods of diagnosis of SCCLD have not been established owing to lack of detailed epidemiological studies.

In Nigeria, there have been studies of lung functions in apparently healthy children and among children with asthma. On the contrary, studies on lung functions of children with SCA are few. In one of the few available studies, Vanderjagtet *al* [8] studied lung functions among children and young adults attending the sickle cell clinic at the Federal Medical Center, Gombe and the Jos University Teaching Hospital, Jos and concluded that abnormal lung functions occur in Nigerian children with sickle cell disease compared to controls.

With improved management, the life expectancy of SCA patients has increased significantly over the years. Consequently, an increase in the prevalence of complications of the disease which are associated with chronic morbidities is expected. Pulmonary complications account for significant morbidity and mortality in patients with sickle cell disease as they cause deterioration in lung functions which impact negatively on the quality of life of patients and may lead to death if appropriate intervention is delayed. A study of lung functions in Nigerian children with SCA is desirable to supplement the existing knowledge on the condition within the locality. This measure will enhance the understanding of the progression of morbidities associated with the disease.

Methods

The study was hospital-based, and the primary subjects were children aged five years to twelve years with SCA diagnosed by cellulose acetate electrophoresis (HbSS)

and attending the Paediatric Sickle Cell Clinic at the Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos. The study was conducted over a period of three months.

Apparently healthy children with haemoglobin genotype AA (HbAA), who have no symptoms or signs attributable to an acute illness in the preceding four weeks, and were age and sex-matched were recruited from the routine Paediatrics Clinics as controls. Additional inclusion criteria for the HbSS group included steady state (defined as the absence of any crisis in the preceding four weeks, no recent drop in the haemoglobin level and absence of any symptoms or sign attributable to an acute illness [9]), absence of acute respiratory diseases such as coryza and pneumonia and lack of medical history suggestive of bronchial asthma. Children with SCA and the controls who had a structural abnormality of the thoracic cage, history of medications which may affect lung functions such as steroids, overt mental subnormality, co-existing HIV infection and presence of congestive cardiac failure were excluded from the study.

A cross-sectional design was used for this study. The minimum sample size to measure the proportion of sickle cell anaemia children with lung function abnormality as against children without sickle cell anaemia was calculated using the formula:[10] $N = (Z_{\alpha/2} + Z_{1-\beta})^2 (\sigma_1^2+\sigma_2^2) / \mu^2$
Where: N = estimated sample size, $Z_{1-\beta}$ = One sided percentage point of the normal distribution corresponding to 100% minus power, (1.96 for 95% power), $1 - \beta$ = power = 95%, $Z_{\alpha/2}$ = percentage point of the normal distribution corresponding to the (two-sided) significance level = 1.96 (95% level of significance), σ_1 =standard deviation for cases which is 0.194, σ_2 = standard deviation for controls which is 0.241 and μ = the difference to be detected between the means of the two samples = 0.15.

The average monthly clinic attendance at the Sickle Cell Clinic was 110, out of which there were about 60 children aged 5 to 12 years. Further stratification of the 60 children showed that 18 were aged 5 to 6 years, 18 were aged 7 to-8 years, 12 were aged 9 to 10 years while 12 were aged 11 to 12 years. This pattern gave a distribution ratio of 3: 3: 2: 2. The average male to female ratio in these distributions was about 1.1: 1. To avoid lopsided clustering of subjects around a particular age or sex, the calculated sample size was stratified according to the distribution pattern of children attending the follow-up clinic. All the children with SCA attending Sickle Cell Clinic within the study period and who met the study criteria were recruited. Age- and sex-matched healthy controls (HbAA) were recruited from the Dermatology Clinic and other follow-up clinics.

Ethical approval was obtained from the Ethics Committee of LASUTH, before the commencement of research. All recruitments were made following written informed consent. Data were collected from the child and the caregiver in all instances. The questionnaire was administered principally in English language and

translated to the local languages including Pidgin English as each case demanded. After that, patients were physically examined and the findings, including the relevant anthropometric parameters, were entered into the study proforma.

Socio-economic status of each subject was determined using the method recommended by Oyedeji. [11] After that, the children were re-classified into upper (classes I and II), middle (class III) and lower (classes IV and V) socioeconomic strata.

Measurement of Forced Expiratory Volume in one second (FEV_1)

Forced Vital Capacity (FVC) and Peak Expiratory Flow Rate (PEFR): This was measured using One-Flow Spirometer (Clement Clerk International® England). Hygiene was strictly observed by using one mouthpiece per child. A universal sterilizable mouthpiece with mouth end diameter of 22 millimetres was used. At the end of each day, the mouthpieces were rinsed with cetrimide and after that autoclaved in preparation for the next day's use. The measurement of FEV_1, FVC and PEFR were done with the One-Flow Spirometer.

Spirometric tests: These were performed in the Consultant Outpatient Clinics for the subjects and the controls using the One-Flow Spirometer (Clement Clerk International®, England). The One-Flow Spirometer is a digital, light weight, hand held spirometer which can be held comfortably by a child aged five years and above. It has an inlet through which the child can blow air into the spirometer, and a small digital screen where the values obtained are displayed.

Detachable universal sterilizable mouthpieces were included in the spirometer pack. Respiratory function tests were performed using the spirometry system to measure the FEV_1, PEFR, FVC, and FEV_1/FVC ratio. The values for three completed attempts were recorded for each child. The highest of the best three readings was taken as the result of each test. [12] Predicted FEV_1, PEFR, FVC, and FEV_1/FVC ratio values, using the formulae obtained from normal Nigerian Children [13] were compared to the observed values for the purpose of assessing the pulmonary functions.

The results of spirometry may depict normal, obstructive, restrictive, or mixed lung functions. The pulmonary functions of each pair of subject and control were classified into four categories based on the criteria of the American Thoracic Society: [14]

a) Normal function was defined by FVC and FEV_1 not less than 80% of predicted values and an FEV_1/FVC ratio less than 70% of the predicted value.
b) Obstructive was defined by FEV_1 less than 80% of predicted value for age, sex and height and an FEV_1/FVC ratio less than 70% of the predicted value.
c) Restrictive disease was defined by FVC less than 80% of predicted value for age, sex, height and race in the presence of FEV_1/FVC ratio not less than 70% of the predicted value.

d) Mixed obstructive/restrictive lung disease was suspected when there is a reduction in FVC below 80% of predicted value for age, sex, height and race in the presence of FEV1/FVC ratio less than 70% of predicted value.

All the data were entered into a standard research proforma, and the statistical analysis was done using the SPSS software version 17.0. Continuous variables were expressed as means and standard deviations (SD) while categorical variables were expressed as percentages. The differences in categorical variables were compared using the Chi-Square test while the Student's t-test was used to compare the means and standard deviations of continuous variables. The level of statistical significance was set at p values less than 0.05.

Results

Characteristics of the study populations

A total of 200 children, 100 each with genotype HbSS and HbAA were studied over a period of four months. The age groups 5 -6 years and 7-8 years formed 30% each of the total population of subjects. The groups of 9-10 years and 11-12 years each accounted for 20% of the study group. There were 50 males and 50 females in each study group. Approximately a third (34.0%) of the subjects belonged to the upper socio-economic strata while 45% and 21% belonged to the middle and lower socio-economic strata respectively. The distribution of the children in the HbSS group according to socio-economic stratification was as follows: upper (24.0%), middle (51.0%) and lower (25.0%) classes. In the HbAA group, 44.0%, 39.0% and 17.0% belonged to the upper, middle and lower classes respectively. The observed difference between the two groups regarding the distribution by socio-economic strata was statistically significant ($p = 0.011$).

Pulmonary function tests of subjects

Table I shows pulmonary function test values of subjects. In both males and females, the mean PEFR values were higher among the controls compared to the HbSS group, but the observed differences were not significant ($p = 0.066$ and 0.370 for males and females, respectively). The mean FVC and FEV_1/FVC ratio values of males and females were also not significantly different for the HbSS ($p = 0.36$ and 0.085 respectively) and HbAA groups ($p = 0.35$ and 0.48 respectively).

Males in the HbAA group had significantly higher mean FEV_1 values compared with their HbSS counterparts ($p = 0.001$). Irrespective of gender, the mean PEFR and FEV_1 values were significantly higher in the HbAA group compared with the HbSS group ($p = 0.048$ and $p = 0.000$ respectively). The lung function indices were comparable among the males and females subjects within the HbSS group. A similar pattern was also observed in the HbAA group.

Table I: Pulmonary function test values of study subjects

Pulmonary Function Tests	HbSS Mean (SD)	HbAA Mean (SD)	T	p – values
PEFR (L/m)				
Males	213.70 (44.40)	234.30 (60.64)	1.938	0.066
Females	216.20 (56.58)	226.30 (55.61)	0.900	0.370
Males and Females	214.95 (50.62)	230.30 (58.03)	1.994	0.048*
FEV_1 (L)				
Males	1.28 (0.24)	1.48 (0.34)	3.416	0.001*
Females	1.33 (0.36)	1.48 (0.44)	1.879	0.063
Males and Females	1.30 (0.31)	1.48 (0.39)	3.532	0.000*
FVC (L)				
Males	4.03 (17.89)	1.70 (0.43)	0.920	0.360
Females	4.12 (18.17)	1.71 (0.50)	0.937	0.351
Males and Females	4.07 (17.94)	1.71 (0.47)	1.320	0.188
FEV_1/FVC (%)				
Males	85.88 (5.12)	87.60 (4.78)	1.736	0.086
Females	85.62 (4.81)	86.28 (4.59)	0.702	0.485
Males and Females	85.75 (4.95)	86.94 (4.71)	1.742	0.083

SD - Standard Deviation *Statistically significant

Distribution of individual criterion for diagnosing pulmonary abnormalities among subjects

Comparison of some selected spirometric parameters which were used as criteria for defining pulmonary abnormalities according to socio-demographic characteristics is shown in Table II. Six of the subjects with sickle cell anaemia had abnormal FEV_1 and FVC values while the only child in the control group with abnormal spirometry results had FEV_1 values below 80% of the predicted value. However, significant differences were only observed in the FVC measurements of the HbSS and HbAA groups (p = 0.029).

Pulmonary function abnormalities of subjects

The prevalence of abnormalities of pulmonary functions obtained from spirometry is shown in Table III. Six subjects in the HbSS group had spirometric profile suggestive of restrictive lung disease with a prevalence of 6% in the HbSS group while none in the HbAA group had a restrictive pattern (p = 0.029). No child in the HbSS and HbAA groups had spirometric profile suggestive of obstructive lung disease or mixed restrictive/obstructive disease.

Table II: Distribution of individual criterion for diagnosing pulmonary abnormalities among study subjects

Pulmonary Function Tests	HbSS	HbAA	p-values
FEV_1 (%)			
<80% of predicted value	6 (6.0)	1 (1.0)	0.118
≥80% of predicted value	94 (94.0)	99 (99.0)	
FVC (%)			
<80% of predicted value	6 (6.0)	0 (0.0)	0.029*
≥80% of predicted value	94 (94.0)	100 (100.0)	
FEV_1/FVC (%)			
<70% of predicted value	0 (0.0)	0 (0.0)	1.000
≥70% of predicted value	100 (100.0)	100 (100.0)	

*** Statistically significant**

Discussion

The data used in the present study were obtained from children with SCA in steady states. The mean FVC was lower in HbSS subjects compared with the controls, although without statistically significant difference. This finding was consistent with the findings from previous studies.[15 - 19] Endothelial hypoxic injury, due to hypoventilation during severe crises affecting the lungs and the chest wall, can eventually result in fibrotic lung injury and reduce the FVC in children with SCA. [20]

The mean FEV_1 among children with SCA, irrespective of gender, of 1.30L in the present study was lower than 1.70L reported by Onigbinde [17] in a similar group of children with SCA at Oshogbo and Ile-Ife in the year 2006. The disparity in the age range of the subjects in both studies may account for the observed differences in the mean values; the upper age limit for the present study was 12 years while it was 15 years in the study done by Onigbinde. [18] It is plausible that the lower mean FEV_1 observed in the present study, was due to the younger age of the children studied compared to the survey done by Onigbinde. [18] Since FEV_1 is directly related to height, weight, age and lung sizes, it is expected that older children should have higher values of FEV_1. Also, the observed difference could be an effect of the smaller sample size of 74 subjects used in the earlier study compared with 100 subjects in the present study as smaller sample sizes are known to give exaggerated sample mean values. [21]

Table III: Prevalence of pulmonary function abnormalities among study subjects

Abnormal lung function	HbSS	HbAA	p-values
Obstructive Lung Defect			1.000
Affected	0 (0.0)	0 (0.0)	
Not affected	100 (100.0)	100 (100.0)	
Restrictive Lung Defect			0.029
Affected	6 (6.0)	0 (0.0)	
Not affected	*94 (94.0)*	*100 (100.0)*	

Values in parenthesis are % of number in group

FEV_1, a timed subdivision of FVC in the first second is a measure of air flow rate in the airways. The mean FEV_1 was higher in controls than in the children with SCA in the present study. The lower values in the HbSS group may be explained by the ongoing subclinical inflammatory process within the respiratory system of children with SCA. [22, 23] The ongoing inflammation may result in airway hyper-reactivity, thereby causing spasm of the bronchial smooth muscle and consequently, reducing the diameter of the bronchioles. The reduced bronchial diameter results in reduced airflow rate which translates to reduced FEV_1.

The mean PEFR was lower among children in the HbSS group than the HbAA group. This observation corroborates reports from earlier studies.[7, 8, 16 - 19, 24] This is because PEFR is dependent on the size of the lungs, lung compliance, rib cage size and mobility. Therefore, reduced PEFR values may result from repeated pulmonary hypoxic injury from pneumonia, acute chest syndrome and pulmonary infarction associated with SCA. [19]

The study aimed to determine the pattern of lung function abnormalities among children with SCA. The two types of abnormalities identified known in SCA include obstructive and restrictive diseases. The basis for obstructive disease in children with SCA is chronic hypoxia and ongoing subclinical inflammation in the respiratory tract of children with SCA.

The zero prevalence of obstructive disease herein reported agrees with an earlier study conducted in southwestern Nigeria, which also reported zero prevalence of obstructive lung defect. [18] On the other hand, Sylvester *et al*. [17] reported a prevalence of obstructive disease of 4.5% among black Americans. In another study of African–Americans, [24] a much higher prevalence rate of 35% was reported. It is noteworthy that the upper

age limit in the study of African–Americans, [24] was 15 years (three years older than the subjects in the present study). However, it is doubtful if that factor could sufficiently explain the large difference in the prevalence rates. Furthermore, a much smaller sample size of 63 was used in the study of African–Americans, which has the risk of generating spuriously high prevalence rates. [21] Another explanation for this observation may be racial differences in the two groups studied. Race is an important determinant of lung function. Previous studies have demonstrated that, on the average, equations for predicted values of pulmonary function tests based on the data generated among white subjects tend to overestimate the FEV_1, and FVC by 12%. [25] Although all our data were corrected for race before analysis, the likelihood of the persistent of a differential pattern cannot be ruled out.

Six children in the HbSS group had features suggestive of restrictive diseases in the present study. Restrictive lung disease connotes interference with the ability of the lungs to expand. Restrictive lung dysfunction probably reflects the infarctive effect of recurrent vaso-occlusive crises affecting the lungs and the rib cage. The resulting lung fibrosis and rib infarction restrict lung expansibility, thereby reducing its volumes and capacities. The six percent prevalence of restrictive lung disease in the current study agreed with the findings of the survey conducted by Sylvester *et al.*, [17] in which 6.3% of the children surveyed had restrictive lung abnormality. This pattern of lung dysfunction among children with SCA is still a matter of continuing investigation. While some workers have reported high prevalence among children and adolescents, [18, 20,22], others have emphasised its rarity. [18]

Conclusion

The mean values of PEFR and FEV_1 were significantly lower among children with SCA compared to the controls. The present study suggested that restrictive pattern of lung functions was the commonest lung function abnormality among children with SCA with a prevalence of 6.0%. There is a need for routine evaluation of pulmonary functions during follow-up visit of children with SCA for early detection of lung volume abnormalities and subsequent prompt interventions to correct such abnormalities.

Plethysmography, a vital tool in the diagnosis of restrictive lung abnormality was not used because it is not available at the study centre. Spirometry, while excellent for the diagnosis of obstructive disease, is at best, a screening tool for restrictive diseases. Predicted standards of lung function indices for children in the sub-region are yet to be generated. Consequently, the observed values among subjects in current study were only compared with predicted values derived using the values of apparently normal Nigerian school children obtained by Oduwole *et al.* [13] which are similar to the controls used in the present study.

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Authors' Contribution: The study was conceived by all the authors. The data was collected by FOA

and ASO while NOF and ASO analysed the data. ASO wrote the initial draft of the manuscript while all the authors reviewed and approved the final version of the manuscript.

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