Respiratory symptoms and ventilatory function tests in Nigerian adults with sickle cell anaemia

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Abstract

Background: Sickle cell disease (SCD) is one of the most common genetic disorders among Africans. Pulmonary complications of Sickle cell anaemia (SCA), both acute and chronic are the leading causes of morbidity and mortality in these patients. This study was aimed to determine the frequency and pattern of respiratory symptoms and ventilatory function among SCA patients in Nigeria.

Material and Methods: In this cross sectional study, Respiratory symptoms frequency, Forced vital capacity (FVC), Forced expiratory volume in one second (FEV1), FEV1/FVC ratio, Forced expiratory flow between 25% and 75% of FVC, were determined in 50 SCA subjects and compared with values in 50 controls.

Results: The SCA patients had more respiratory symptoms and significantly lower ventilatory function tests values compared to the matched controls ($p<0.05$). The overall prevalence of at least one respiratory symptom among the sickle cell anaemia patient was (78%). The most common symptom was chest pain (58%). SCA patients had significantly lower mean ventilatory function indices than the control subjects with $P<0.05$ for FVC, FEV1 and FEF 25%-75%.

Twenty seven subjects (54%) of the SCA patients had abnormal lung function test compared with only two (4%) of the control subjects. Out of these, eighteen subjects (36%) had a restrictive pattern. There was no significant difference in the ventilatory function indices between SCA patients with respiratory symptoms and those without respiratory symptoms.

There was no association between the level of stable or foetal haemoglobin and the ventilatory function indices, (for each $P>0.05$).

Conclusion: The most common respiratory symptoms in the subjects with SCA were chest pain and breathlessness. More so, impairment of ventilatory functions indices (PEFR, FVC, FEV1, FEF25%-75%) was common. The most common pattern of ventilatory function in adult sickle cell anaemia subjects is restrictive while the presence or absence of respiratory symptoms was not associated with changes in ventilatory function indices. The level of stable HB and foetal Hb were not associated with changes in the ventilatory function indices.

Keywords: Respiratory symptoms; Ventilatory functions; Sickle cell anaemia

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Introduction

Sickle cell disease (SCD) is one of the most common genetic disorders among Africans. Of the children born annually with haemoglobinopathies worldwide, 61.4% have SCD and are all of African descent.[1]

Pulmonary dysfunction is a common cause of morbidity and mortality among individuals with sickle cell disease (SCD).1 Acute pulmonary complications, such as acute chest syndrome (ACS), predominate in children, while chronic lung disease is more common in adults with SCD. Acute chest syndrome occurs in ~50% of individuals with SCD over the course of their lifetime. Repetitive episodes of ACS may lead to sickle chronic lung disease, which is characterized by a restrictive pattern on pulmonary function testing.[2] Sickle chronic lung disease is the cause of death for 20% of adults with SCD.[3]

Some authors have alluded to the fact that there were high numbers of respiratory symptoms (cough and wheeze) among patients with sickle cell disease which may also trigger acute painful episodes.[4]

The lung is among the major organs involved in sickle cell anaemia.[5,6] Pulmonary complications account for a large proportion of deaths among patients with sickle cell anaemia. According to the cooperative study of sickle cell disease (CSSCD), more than 20% of adults had fatal pulmonary complications of sickle cell anaemia.[7] Pulmonary complications, both acute and chronic, are the leading causes of morbidity and mortality in SCA patients. [7-9]

Pulmonary manifestations in SCA include acute chest syndrome, airway obstruction, restrictive lung disease, thromboembolism, and sickle cell chronic lung disease, which in its most severe form ultimately lead to pulmonary hypertension (PH).[10-12] Also in the spectrum of manifestation is chronic dyspnoea, asthma or recurrent wheezing without a diagnosis of asthma, pulmonary fibrosis, and sleep-disordered breathing which encompasses two broad and sometimes overlapping groups (Obstructive sleep apnoea and Nocturnal hypoventilation).

Hypoxia during any major respiratory insult is thought to contribute to diminished phagocytosis by pulmonary alveolar macrophages, the defensive cells of the ventilation-perfusion unit. As a result, bacterial pneumonia is common and frequently involves the middle and upper lobes of the lungs and may be complicated by bacteraemia which may in turn cause meningitis. These infections are estimated to be 20 to 100 times more frequent in patients with sickle cell disease than in persons with a Normal genotype.

It is also noted that the deficiency of properidin system leading to reduced opsonisation of capsular organisms as reason for frequency of infections

Most of the studies on the ventilatory function in patients with sickle cell anaemia have yielded a variable spectrum of abnormalities, including restrictive lung disease in a majority of cases, obstructive disease, and hypoxemia. It is worthy of mention that previous studies have documented characteristic patterns of pulmonary function in sickle cell anaemia patients. Some have also

demonstrated lower levels of spirometric indices such as FEV1 and FVC in Sickle cell anaemia patients when compared with normal subjects.

Despite the significant contribution of pulmonary disease to SCA-related morbidity and mortality, pulmonary function test (PFT) abnormalities are not well described in adults with SCA in Nigeria especially in the South East sub region. The aim of this study was to determine the prevalence and pattern of respiratory symptoms as well as the ventilatory function in patients with sickle cell anaemia.

Materials and Methods

Ethical approval

Ethical clearance for the study was obtained from the Health Research Ethics Committee of the University of Nigeria Teaching Hospital, Ituku–Ozalla, Enugu.

Study design

This work was a cross sectional study. SCA patients attending the SCA clinic at the University of Nigeria teaching hospital Enugu, South East Nigeria, were recruited over a one year period between January 2017 and February 2018. Every alternate patient attending the clinic was recruited if he or she gave written informed consent and did not have any exclusion criterion.

Majority of the patients attending were of same tribe (Igbo). The clinic runs once weekly and adult patients 18 years and above are usually in attendance.

Sample size

The sample size was calculated using the fisher's formula for estimating minimum sample size in health studies at 3.1% prevalence of sickle cell anaemia obtained from a study in Ibadan, south-western Nigeria. Considering 0.05 as the absolute sampling error that can be tolerated, 46 subjects were estimated but 50 patients were recruited and studied during this period to improve the accuracy of the study results and analysis.

Study population

The study population of 50 was drawn from an equal number of controls (50) who were comparable to the SCA patients in age, sex, height were recruited randomly and studied alongside the study population if they gave written informed consent and did not have any of the exclusion criteria. On the average about four SCA patients and four control subjects were recruited and studied weekly. The matching of the controls was a rigorous procedure carried out by simple observation first and then actual measurements of the parameters to be matched. The same exclusion criteria were used for the cases as well the control subjects.

All patients and controls recruited were assessed using a structured pre tested respiratory questionnaire to obtain their clinical and anthropometric data. They also had genotype and foetal haemoglobin assessment using the D10 high performance liquid chromatography machine. Their haemoglobin levels were assessd using the haemoglobinometer.

Spirometry testing was performed using a digital Spirometer (Spirolab III) Medical International Research, Italy (September, 2011) after the procedure was thoroughly explained to the patients and controls according to the ATS/ERS guidelines. Measurements were performed with the Patients in sitting position without nose clip. Forced expiratory manoeuvres were repeated until three accepted and reproducible tests were obtained. The spirometer was calibrated every day of the study using the calibration syringe following the calibration procedures already set by the equipment Manufacturer.

The FVC, FEV1, FEV1/FVC and FEF25-75% were determined for each subject and control. All the ventilatory function tests for the subjects and controls were conducted between 9.00 am and 12.00 noon.

Statistical analysis

The collated data was coded, entered and analysed using Microsoft Excel 2007 and Statistical Package for Social Science (SPSS) version 21 Descriptive statistics was used for continuous variables expressed as means and standard deviations while categorical variables were expressed as frequencies and percentages. The inferential statistics used were Independent Samples t-test, the Mann-Whitney U test, Chi-Square test, Fishers Exact test and Spearman Correlation. Specifically, the t-test was used for comparisons involving normally distributed continuous variables, while the Mann-Whitney U test was used for comparisons involving continuous variables that were not normally distributed. The Chi-Square Test was used for analyses involving two categorical variables while Fishers Exact Test was used when a Chi-Square Test assumption was not met by the data. Spearman Correlation was used to ascertain relationship of two numerical variables where the data was not normally distributed. Statistical decision rule was at 5% level of significance. Hence, significant difference was concluded when p-value was less than .05, ($p<.05$).

The frequencies of respiratory symptoms were compared between SCA patients and the controls. The mean ventilatory indices of the SCA patients were compared with the values found in the matched controls

The reference equations will be used to calculate ventilatory function values in SCA patients and control subjects. Those with FVC less than 80% predicted with FEV1/FVC% normal or increased were classified as having restrictive lung impairment while those with FEV1/FVC less than 70% and those with FEV1 less than 80% predicted were classified as having obstructive functional lung impairment. Patients with ventilatory function values above 80% predicted were classified as normal.

Results

Fifty eligible SCA subjects were recruited during this period and were studied with fifty controls. There were 24 SCA males representing (48%) of the total and 26 SCA females representing (52%) of the total. This was the same for the control group.

The age of the cases ranged from 18-46 years with mean and standard deviation of 26.28 ± 6.58 years and modal age group of below 25 years (42.0%); this was comparable to the controls. There were more students among the participants.

There was no statistically significant differences in the mean heights ($p=0.839$), however there was statistically significant differences in the mean weights ($p<0.001$) and BMI ($p<0.001$) between the cases and control subjects.

The mean and standard deviation of stable Hb and foetal Hb for the SCA patients were 8.47 ± 1.16 g/dl and 6.96 ± 5.22% respectively (Table 1).

Table 1: Mean Stable Hb and Foetal Hb for the Cases.

Measured Variables	Cases (n=50) Mean ±SD	Control (n = 50) Mean ±SD	T	df	p-value
Stable (Hb g/dl)	8.47 ± 1.16	-	-	-	-
Foetal Hb(%)	6.96 ± 5.22	-	-	-	-
HB=Haemoglobin; SD=Standard deviation					

The most frequent respiratory symptoms in SCA patients were chest pain, breathlessness and cough with frequencies of 58%, 46% and 36%, respectively. Compared with males, females reported a significantly higher prevalence of breathlessness (29.2% vs. 61.5%; p=0.022). Beyond breathlessness, there were no significant sex differences in the frequency of respiratory symptoms among the cases.

The mean FVC, FEV1, PEFR and FEF25-75 in the SCA patients were significantly lower in the SCA patients than in the control group with p<0.05 for each parameter.

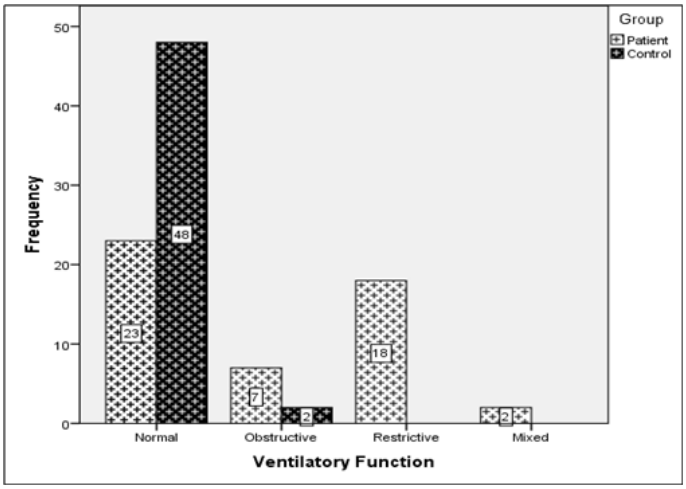
The mean ratio of FEV1 to FVC (FEV1/FVC) was higher in the control group (84.57 ± 7.45%) than the SCA patients (83.85 ± 7.45%) but the difference was not statistically significant (p=0.693).

The mean percentage predicted values for FVC, FEV1 and PEFR among sickle cell anaemia patients (86.62 ± 18.73%, 89.34 ± 18.30%, and 93.85 ± 24.92, respectively) were lower than in the control population (104.16 ± 13.63%, 109.10 ± 13.39%, and 111.69 ± 20.1%, respectively). The difference in the observed means for each of the parameters between the two study groups achieved statistical significance with p<0.001.

Overall, a total of 27(54%) SCA patients had abnormal lung function test compared with only 2(4%) of the control subjects (Figure 1). The difference was statistically significant (P<0.001).

Comparatively, the Non symptomatic patients had higher values but the differences were not statistically significant. PEFR (p=0.198), FVC (p=0.667), FEV1 (p=0.228), FEV1/FVC (p=0.461), and FEF25-75 (p=0.239).

Figure 1: *Pattern of ventilatory function.*



Comparison between the SCA patients with normal and abnormal ventilatory function revealed a significant difference both for stable Hb (p=0.030) and foetal Hb (p=0.016). The patients with normal ventilatory function had higher mean in the stable Hb (8.85 ± 1.09 g/dl) and foetal (Hb 8.89 ± 6.11%) than those with abnormal ventilatory function (stable Hb 8.15 ± 1.14 g/dl, foetal Hb 5.31 ± 3.68%) (Table 2).

Table 2: Pattern of ventilatory function.

	Normal V F Mean ± SD	Abnormal V F Mean ± SD	Mann-Whitney U	p-value
Stable Hb(g/dl)	8.85 ± 1.09	8.15 ± 1.14	200	0.03
Foetal Hb(%)	8.89 ± 6.11	5.31 ± 3.68	187	0.016
P value based on: Mann-Whitney U test; V F= ventilatory function SD= Standard deviation				

Furthermore, there was no statistically significant correlation between the foetal/stable Hb and the measured ventilatory function parameters viz; Stable Hb and PEFR (p=.433), FVC (p=.321), FEV1 (p=.147) and FEF25-75 (p=.154); and likewise between the ventilatory indices and foetal Hb PEFR (p=.125), FVC (p=0.154), FEV1 (p=.151) and FEF25-75 (p=.052) (Table 3).

Table 3: Relationship between Ventilatory Function Indices and Stable and Foetal Hb.

	PEFR	FVC	FEV1	FEF25-75	187
Stable HB	Correlation Coefficient	0.113	0.143	0.1	0.154
	p-value	0.433	0.321	0.3	0.287
Foetal HB	Correlation Coefficient	0.125	0.154	0.2	0.052
	p-value	0.386	0.284	0.3	0.718
P value based on Spearman Correlation					

Discussion

This study revealed that majority of the patients with sickle cell anaemia were symptomatic (had at least one respiratory symptom). The most common respiratory symptom was chest pain followed by breathlessness. The study also showed that more than half of the subjects had impaired ventilatory function and the pattern of ventilatory dysfunction found among these patients was largely restrictive.

This finding was corroborated by previous researchers who found chest pain and breathlessness as the most common respiratory symptoms in SCA patients. The chest pain could be as result of a subclinical acute chest syndrome or rib infarction. Most SCA patients have difficulty with opsonised organism and this may lead to recurrent chest infection which may not have been apparent during the time of study. It's also possible that the background or past acute chest syndrome may have been responsible for the increase prevalence of breathlessness in the cases.

This study clearly showed that most of the SCA patients had an abnormal ventilatory pattern with most being restrictive. Patients with respiratory symptoms were generally found to have lower ventilatory parameters than those without respiratory symptoms this finding is not unexpected and could suggest that patients with respiratory symptoms have more affectation of the respiratory tract due to chronic micro thromboembolism as well as impaired immune function which occurs in SCA patients. Further formal lung function laboratory studies with transfer factor tests preferably in a larger population of SCA individuals will be necessary to establish the significance of this finding.

In this study as well, it was found that cases with lower haemoglobin and foetal haemoglobin had a much lower ventilatory indices. It is also possible that those with a lower Hb may have had more crises in which the lungs were equally affected. Considering SCA as systemic problem, it is no surprise that the ventilator indices were lesser compared to the control group. It's also noted that SCA patients with a higher foetal Hb had lesser symptoms and most likely and of course may explain the finding of lower ventilatory indices in those with lower foetal Hb

The limitation of this study is that it was not possible to study the diffusion capacity of the lungs to carbon monoxide due to lack of such facilities as well as the overwhelming difficult logistics in procuring the equipment

This study was a cross sectional study so it could not look at the rate of possible decline of lung function indices as a result of the disease.

It was also not possible to determine the exact pathological changes responsible for the ventilatory dysfunction found among the studied Sickle Cell Anaemia patients as lung biopsies were not done.

It is hoped that this study of ventilatory functions in SCA patients will stimulate further research in this regard more especially in the area of identifying the rate of decline in ventilator function among this patient population.

Conclusion

The most common respiratory symptoms in the subjects with SCA were chest pain and breathlessness. More so, impairment of ventilatory functions indices (PEFR, FVC, FEV1, FEF25%-75%) was common. The most common pattern of ventilatory function in adult sickle cell anaemia subjects is restrictive while the presence or absence of respiratory symptoms was not associated with changes in ventilatory function indices. The level of stable HB and foetal Hb were not associated with changes in the ventilatory function indices.

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