ORIGINAL ARTICLE

PULMONARY FUNCTIONS IN ADOLESCENTS WITH SICKLE CELL ANAEMIA: A CASE-CONTROL STUDY

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ABSTRACT

Introduction: Sickle cell diseases are one the commonest hemoglobinopathies in the central and southern India. About 20-30% deaths in Sickle cell anaemia (SCA) patients occur due to respiratory disorder. Studies had shown that highest mortalities in Sickle cell disease (SCD) patients is due to pulmonary complications. Pulmonary function test (PFT) assess the functional status of respiratory system so the study was planned to determine the changes in lung functions in SCA adolescent patients and to compare it with age, gender and body mass index (BMI) matched healthy adolescent individuals using Spirometry.

Material and methods: 60 adolescent subjects (30 cases (SCA) and 30 controls) were included in the study whose pulmonary function test parameters using spirometry were measured.

Results: 22 (73.4%) had abnormal spirometric results, 18 (60%) had restrictive pattern, 2(6.6%) had obstructive pattern, 2(6.6%) had mixed pattern and 8 (26.6%) had no abnormality.

Conclusion: Pulmonary functions are significantly decreased in sickle cell anaemia adolescents. Possible restrictive pattern is the predominant spirometric abnormality in these patients.

Keywords: Sickle cell anemia, Sickle cell disease, Spirometry, Pulmonary function test, restrictive abnormality

INTRODUCTION

Sickle-cell disease (SCD) is one of the commonest hemoglobinopathies in the central and southern India.[1] It is a genetically transmitted hemoglobinopathy which is autosomal recessive in nature which may affect any organ or system of the body.[2] Hemolytic anaemia, granulocytosis, vaso-occlusion, acute chest syndrome (ACS), pulmonary infarction and pneumonia are seen in SCD patients[3]. Pulmonary function test (PFT) assesses the functional status of respiratory system.[4] Spirometry detects, quantifies & monitors the disease that limits ventilatory capacity of the lung.[5] Adolescent group, which consists of children in the age group of 10-19 years constitutes about 23% population of India.[6] About 20-30% deaths in Sickle cell anaemia (SCA) patients occur due to respiratory ailments that requires hospitilization.[7] Many complications in SCA are manifested in childhood and adolescence group which may result in repeated lung damages caused by episodes of pulmonary vasocculsion including pulmonary hypertension, pulmonary vasocculsion and ACS.[7] Studies have shown that highest mortalities in SCD patients is due to pulmonary complications such as pulmonary hypertension and ACS.[8] Considering the number of circulatory and pulmonary dysfunctions in SCA patients, the lung functions are important to analyse in these patients since they remain underdiagnosed by physicians. With this background, the current study was planned to determine the changes in lung functions in SCA adolescent patients using spirometry.

METHODOLOGY

The study was conducted during July 2012 to December 2014. The study was carried out after approval from the institutional ethical committee and with fully informed written consent from the subjects, in a tertiary care teaching hospital in central India. This was an observational case control study. The following two groups of subjects were included: 30 adolescent SCA patients and 30 healthy control subjects. A total of 60 consecutive subjects were included in the study depending on the criteria till the desired sample size of each group was met. The patients were recruited as per the following criteria:1. SCA: Adolescent boys and girls aged between 10 to

19 years of age diagnosed with HbSS pattern SCA. 2. Healthy control subject: Age, gender and body mass index (BMI) matched healthy adolescent who was a 1st or 2nd degree cousin of sickle cell patients and having confirmed negative sickling test. Subjects with cardiac disorder, history of smoking, gross abnormalities of the vertebral column or thoracic cage, neuromuscular disease, malignancy, known infection with human immunodeficiency virus (HIV), acute respiratory infections, extreme BMI, history of any previous pulmonary and cardiac surgery or clinical examination suggestive of any other respiratory or cardiac comorbidity were excluded from the study. Also, acute chest syndrome was a specific exclusion criterion for the SCA group. After detailed clinical assessment all the subjects underwent spirometry (Spirometer - Medical Graphics Corporation, USA; Software: Breeze Suite Version 6.2C). The spirometry was performed and interpreted as per the ATS criteria. The spirometric parameters that were recorded were forced expiratory volume in 1st second (FEV_1), forced vital capacity (FVC), FEV_1 /FVC, Peak expiratory flow rate (PEFR) and Forced expiratory flow - 25% to 75% (FEF25-75%) along with Maximum voluntary ventilation MVV.

Statistical analysis: The pulmonary function test values of all the subjects were analysed. Percentage predicted values of the PFT parameters were recorded except for FEV1/FVC where absolute values were recorded. Following variables were used for statistical analysis: FVC, FEV1, FEF25-75, PEF and MVV. The data was analysed statistically by using graph pad instat 3 software**.** Various statistical measures such as mean, standard deviation (SD), tests of significance and 95% confidence interval (CI) were calculated. Gender difference between the two groups was analysed using chi square test. As the data was non-uniformly distributed, non-parametric test (Mann-Whitney) test of significance was used. Thus, inter-group comparison of mean differences in FVC, FEV1, FEF25-75, PEF, MVV was done by using Mann-Whitney test. $P < 0.05$ was considered statistically significant.

RESULTS

There was no significant difference in age, gender or BMI in between the two groups viz. the adolescent sickle cell patient group (Cases) and the healthy control group (Control) as is depicted in table no. 1 and table no. 2. The pulmonary function test parameters and the type of spirometric abnormality are shown in table no. 3 and table no. 4 respectively. 22 (73.4%) had abnormal spirometric results, 18 (60%) had possible restrictive pattern, 2(6.6%) had obstructive pattern, 2(6.6%) had mixed pattern and 8 (26.6%) had no abnormality. Thus, the most common type of spirometric abnormality was a possible restrictive pattern. Table no. 5 represents the severity of spirometric abnormality which shows the spirometric abnormality in most of the cases to be of moderate severity.

Table 1: Age and BMI in adolescent SCA patients and healthy controls

Variables	Cases (SCA patients)	Control	p-Value
	Mean ± SD	Mean ± SD	
Age	14.933±3.321	15.1±2.440	0.8579
BMI	17.032±3.427	18.885±4.917	0.4463

Table 2: Gender wise distribution between adolescent SCA patients and healthy controls

Gender	Cases (SCA patients)	Control	Total
Male	17 (28)	17 (28)	34 (57)
Female	13 (22)	13 (22)	26 (43)
Total	30 (50)	30 (30)	60 (100)

Figure in the bracket indicate percentage.
Chi square =0.0000 p=1 df=1

DISCUSSION

The present study was designed to compare the pulmonary functions in adolescents with SCA with age, gender, and BMI matched healthy individuals. A total of 60 subjects i.e. 30 adolescent healthy individuals and 30 adolescents with SCA (HbSS) participated in the study. In our study, there were 17 males and 13 females in both cases and control group. Demographic details of the subjects in both groups (age, gender and BMI) were matching at baseline hence both the group were comparable. The study analysed the pulmonary functions in adolescent SCA patients and in normal healthy adolescent individuals.

Table 3: Pulmonary function analysis of adolescent SCA patients and healthy controls

Variables % predicted	Cases		Control		p-Value
	Mean ± SD	95% C.I.	Mean ± SD	95%C.I	
FEV1 (Forced Expiratory Volume in 1st Second)	73.1 ± 20.9	65.3-80.9	99.1 ± 18.5	92.2-106.0	<0.0001
FVC (Forced Vital Capacity	75.9 ± 20.0	68.4-83.4	96.4 ± 17.1	90-102.8	<0.0001
FEF25-75%(forced expiratory flow 25-75%)	66.9 ±30.7	55.4-78.4	94.5 ± 21.2	86.6-102.4	0.0007
PEF%	66.4 ± 14.1	61.1-71.7	85.7 ± 12.2	81.2-90.3	<0.0001
MVV%	71.0 ± 20.4	63.4-78.7	93.0 ± 12.4	88.3-97.6	<0.0001

Table 4: Type of Spirometry abnormality based on FEV1/FVC ratio between cases and control

Variables	Cases (%)	Control (%)
Obstructive	2 (6.6)	-
Restrictive	18 (60.0)	2 (6.6)
Mixed	2 (6.6)	-
No Abnormality	8 (26.6)	28 (93.3)
Total	**30 (100)**	**30 (100)**

Table 5: Severity of Spirometry abnormalities based on FEV1 in cases and control

Spirometry abnormality	Control (%)	Cases (%)
No Spirometry abnormality	28 (93.3)	8 (26.7)
Spirometry abnormality as per severity of FEV1		
>70%(mild)	2 (6.7)	4 (13.3)
60-69(moderate)	0	12 (40.0)
50-59(moderate-severe)	0	4 (13.3)
35-49(severe)	0	2 (6.7)
<35(very severe)	0	0
Total	**30 (100)**	**30 (100)**

Pulmonary functions (FVC, FEV1, FEF25-75, PEF& MVV) were statistically significantly decreased in cases as compared with control group.

The findings of the present study suggest that a possible restrictive pattern is the most common spirometric abnormality in patients with SCA.

Table no. 6 shows the major studies on patients with SCA published till date, most of which are in concordance with the findings of the present study depicting restrictive pattern as the predominant spirometric abnormality in these patients.

The probable reason of a possible spirometric restrictive pattern in patients with SCA may be related to peripheral vaso-occlusion, prior rib infraction or vertebral disease causing ineffective inspiration due to chest pain. Also, chest wall discomfort during testing which may be due to vaso-occlusion could lead to a possible restrictive abnormality on spirometry[7]. Bone infract, osteoporosis or osteomalacia in the vertebra causing structural impairments may lead to restrictive pattern[20]. The possible reason for a restrictive ventilatory disorder in these patients is the pulmonary infarction possibly due to vaso-occlusion and fat pulmonary embolism, which may be followed by an event like bone ischemia, with consequent replacement of lung parenchyma with fibrotic tissue.[21]

Two markers of the disease severity i.e. haemolysis and leucocytosis were related to decline in lung volume.[10] Higher leucocyte counts have been an independent risk factor for lower total lung capacity and vital capacity. Adherence of leucocytes to the blood vessel wall results in obstruction of lumen. They also stimulate the vascular endothelium resulting inexpression of ligands for adhesion. This leads to a cascade of events leading to tissue damage, and an inflammatory reaction resulting in further obstruction of capillaries and post capillary venules and thus resulting in a possible restrictive pattern.[10]

Lower lung volumes have also been shown to correlate with markers of chronic hemolysis (lower hemoglobin (Hb), higher baseline reticulocyte count or lactate dehydrogenase (LDH) value). Higher C-reactive proteins (CRP) levels suggestive of chronic inflammation are seen in subjects with lower Hb level, thus possibly playing a role in pathophysiology of the restrictive lung disease.[15]

Functional and structural impairments of pulmonary vessels have been seen due to endothelial dysfunction as a result of impaired arginine-nitric oxide pathway, oxidative stress and tissue damage. Also, interstitial pulmonary fibrosis may be present in transfused SCD patient having iron overload. Abnormal PFT may be due to excess production of proline, polyamines and dysregulated arginine metabolism. High levels of proline and arginase have been shown to have a role in the pathogenesis of pulmonary fibrosis in SCD patients.[22]

Thus, the result of the present study supports the hypothesis that there is significant difference in PFT parameters in adolescent SCA as compared to normal subjects and probability of restrictive ventilator defect in SCA patients.

The limitations of our study are as follows: 1. Symptomatic profile of the patients were not recorded in the current study and hence a correlation of the restrictive spirometric abnormality with a clinical parameter like the number of episodes of acute chest syndrome could not be arrived at. 2. Due to the resource limited settings, whole body Plethysmography and diffusion studies could not be done to confirm the restrictive spirometric abnormality. 3. Bronchodilator reversibility testing to assess airway hyperresponsiveness was not done in the current study.

CONCLUSION

Adolescent SCA patients have reduced pulmonary function test parameters signifying a possible restrictive ventilatory defect and hence pulmonary function assessment is of essentially important in these patients. However, PFT is a physiological test & should be correlated with other tests to confirm the structural abnormalities in patients with SCA. Considering the results of the present study, further studies on comparison of pulmonary functions in various age groups in SCA patients in Indian setup could yield valuable information. Also, future studies correlating pulmonary functions abnormalities with hematological investigations in SCA patients could provide another useful dimension to the possible etiology of restrictive spirometric abnormality.

Table 6: Various studies to assess the pulmonary functions in patients with Sickle Cell Anaemia/ Sickle Cell Disease (SCA/SCD)

Author name	Year /Type of study	Age group studied	Parameters	Results (Type of Spirometry abnormalities)
Present study	2012 Case control	10-19 yrs.	FEV1, FVC, FEF25-75, PEF, MVV	Restrictive predominant
Sylvester K.P et al [9]	2003 case control	64 children with SCD aged 5–16 years and 64 ethnic matched controls were recruited	Functional residual capacity using a helium gas dilution technique (FRCHe) and by whole body plethysmography (FRCpleth). Total lung capacity (TLCpleth), vital capacity (VCpleth), and residual volume (RVpleth) were also measured by whole body plethysmography, FEV1, FVC, FEV1/FVC, and PEF	Restrictive pattern.
Fonseca CSV et al[21]	2009 Cross sectional	50 SCD patients in the age 10 yrs. and above	FEV1, FVC, FEF 25-75%, (pre & post bronchodilator)	predominant Mixed respiratory pattern or combined type, followed by the classical restrictive pattern
Tassel C et al [10]	2010 Cohort Study	Children who were diagnosed as SCA.	VC, FEVI, FRC, FEV1/FVC TLC, DLCO.	Restrictive pattern was predominant.
Ezzat DA et al[11]	2009 observational study	26 paediatric patients with 16 patients with â-Thalassemia & 10 patients with SCD	FVC, FEV1, FEV1/FVC%, FEF 25-75, FEF75, PEF), end systolic diameter, end diastolic diameter, Fractional shortening (FS%), Ejection Fraction (EF%), E/A ratio, Right Ventricular Diameter (RVD) & pulmonary artery systolic pressure (PASP)	PFT reflecting restrictive lung abnormalities. And pulmonary hypertension in â- thalassemia &SCD start early in childhood
Hagag AA et al[12]	2014 case control	40 children with SCA age ranging from 7– 15 years	FEV1, FEV1% FEV1/ FVC ratio, PEFR, PEFR% FEF, FVC, FVC% serum ferritin, serum iron and Total iron binding capacity (TIBC), complete blood count (CBC)	In the present work, there were restrictive spirometric pattern in 75% of studied patients with sickle cell anaemia and mixed obstructive and restrictive pattern in 25% of patients
Oko-Ose JN et al[4]	2012 Case control	60 subjects (30 patients and 30 control groups)	FVC, FEV1, and FEV1/FVC FVC%, FEV1%, and FEV1/FVC% predicted	The lung function declined with age. This work has also shown that the most common pulmonary function test (PFT) abnormality was restrictive disease pattern (76.7%)
Cook J et al[13]	2013 Cross Sectional	25 children aged 7-16 yrs. with electrophoretically confirmed SCD	FEV1, FVC and FEV1/FVC ratio	spirometric abnormalities suggestive of restrictive lung disease with no evidence of obstructive defects
MacLean JE et al[14]	2008 Longitudinal Study	413 children SCD in the age group of 8-18 yrs. -	FEV1, FVC, FEV1/FVC FEF25–75, TLC, and RV.	Restrictive defect. the decline begins in childhood
Williams K et al[15]	2012 Case control	74 controls and 154 SCD subjects with mean age 31yrs.	FVC, FEV1, FEV1/FVC FVC%, FEV%1, and FEV1/FVC%	sickle cell disease tends to have lower lung function parameters than healthy controls consistent with a restrictive defect
Klings ES et al[16]	2006 Cross Sectional	310 adults with Hb-SS were analysed	FEV1, FVC, FEV1/FVC, TLC, RV, and Diffusing lung capacity for Carbon monoxide (DLCO)	Pulmonary functions are abnormal in 90% of adult with Hb-SS. and Restrictive physiology and decreased DLCO.
Molavi MA et al[17]	2011 Cross Sectional	29 subjects (SCA with Acute Chest Syndrome) in the age group of 6-18 years,	FEVI/FVC.	Pulmonary functions abnormal in 79.3% and restrictive pattern, normal pattern (20.7%, 6 cases) and obstructive pattern (6.9%, 2 cases).

Author name	Year /Type of study	Age group studied	Parameters	Results (Type of Spirometry abnormalities)
Hulke SM et al[7]	2011 Cross sectional	20-40 yrs. 133 subjects (SCD)	FEVI/FVC, FVC, FEVI, PEFR, MVV, FEF25-75%, FEF50%, FEF75%.	Restrictive pattern.
Santoli F et al[18]	1998 Cross Sectional	49 subjects (SCD) in the age group of 16–49 yrs.	TLC % pred, FVC % pred, FRC % pred, FEV1 % pred, FEV1/VC %, pred FEF50 % pred, FEF25 % pred, FEF25–75 % pred, (Respiratory resistance) Rrs, KCO % pred TLCO %	Obstructive pattern
Fawibe AE et al [19]	2006 case control	57 SCA were compared with 60 age matched control. The age of patients was in between 18-32 yrs. and of control was between 17-30 yrs.	FVC, FEV1, PEFR	Restrictive pattern predominant.

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