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Original Research Article

Study of Pulmonary Function Tests in Patients with Sickle Cell Disease

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Abstract

Background: Sickle-cell disease (SCD) is a life-long haematological disorder characterized by red blood cells that assume an abnormal, rigid, and sickle shape. Pulmonary involvement is a major cause of morbidity and mortality in patients with SCD. The present study was undertaken to determine pulmonary functions in SCD patients and to compare the pulmonary functions between sickle cell anemia (SCA) and sickle cell trait.

Method: Total 155 patients of SCD were enrolled in the study. A detailed history, clinical and relevant investigations were done for all the patients. Pulmonary function test was performed and findings were compared between SCA and sickle cell trait.

Results: The patients of SCA (HBSS) were 80(51.61%) while that of sickle cell trait (HBAS) was 75(48.38%). There were lower values of FEV1, FVC and PEFR among SS population as compared to AS population with increase in FEV1/FVC ratio. The restrictive pattern of spirometry was more common among sickle cell patients (53.54%). Among SS population in both male (72%) and female (28%) restrictive pattern was common while among AS population most common spirometry pattern was normal spirometry while second most common pattern was restrictive pattern which occurs in 13 patients (39.40%) in males and 20 patients(60.60%) in females.

Conclusion: Chronic pulmonary complications in SCA are common. Abnormal pulmonary function was present in 63.87% of total population of SCD. SCA patients have reduced FEV1 and FVC values, despite this reduction they had significantly increased FEV1/FVC ratio which is keeping a restrictive pattern of pulmonary dysfunction.

Keywords: Sickle-cell disease, Pulmonary function test, Spirometry, Restrictive pattern, FEV1/FVC ratio.

1. Introduction

Sickle cell disease (SCD) is a genetic hemoglobinopathy first described in 1910 [1]. SCD is more prevalent in tribal and central region of India where its prevalence in different communities varies between 9.4–22.2 % [2]. Lung is one of the major organs involved in SCD. Two major forms of clinical lung involvement are acute chest syndrome (ACS) and sickle cell chronic lung disease (SCCLD). These acute and chronic pulmonary complications represent the most common cause of death from SCD in adulthood [3]. Although the pathogenesis of chronic pulmonary disease in SCD has not been clearly defined, recurrent micro vascular obstruction resulting in the development of pulmonary complications are probably the primary mechanisms [4].

Pulmonary complications, including acute chest syndrome (ACS), pulmonary hypertension (PH), and pulmonary fibrosis, account for 20 to 30 % of deaths of SCD patients [5,6]. Even with improved treatment, including the early use of prophylactic antibiotic regimens, judicious transfusions and the administration of hydroxyurea in selected patients, mortality remains high for this population. A multicenter study has listed more than 20% of fatal pulmonary complications in adults [5]. There is no definitive profile for pulmonary function in sickle cell disease as emerged uptill now. As a result, clinicians find pulmonary function tests (PFTs) difficult to interpret in this population and their clinical utility for directing further investigation.

The purpose of present study was to evaluate the relation of clinical and laboratory characteristics to lung function in the SCD population. PFTs were done on subjects recruited as part of the Cooperative Study of Sickle Cell Disease (CSSCD), a cross-sectional epidemiological study. Some of the results of these studies have been previously presented in the form of an abstract at the 47th annual meeting of the American Society of Hematology [7]. Larger scale studies are necessary to elucidate more clearly. Also in this part of the world i.e. Yavatmal where sickle cell disease is highly prevalent, studies are needed to be performed to evaluate the characteristics of lung function in the SCD population.

2. Materials and Methods

The present observational cross sectional study was conducted in 155 patients of sickle cell anemia having age above 12 years. Patients who were admitted in Department of Medicine in SVNGMC hospital, who were coming to sickle cell OPD and patients who were referred from other health centre in district to our institute was included in the study. Patients with sickle cell disease with known pulmonary disease, patients who were smokers and patients with sickle cell crisis were excluded from the study. After obtaining Institutional Ethical Committee approval, all the cases of sickle cell anemia and sickle cell trait were studied during the period of 1st January 2016 to 30th June 2017.

A detailed history, clinical examination and all relevant investigations were done for the entire patients. The pulmonary function test was performed. For pulmonary function test: - MIR Spirolab II (Via Del Maggiolino, 125, 00153, Rome, Italy) was used. PET was recorded at the OP. All the subjects were made familiar with the instrument and the procedure for performing the test. The data of the subject as regards to name, age, height, weight, sex, date of performing the test, atmospheric temperature was fed to the computerized MIR Spirolab. The tests were performed in sitting position. The subject was asked to take full inspiration which was followed by as much rapid and forceful expiration as possible in the mouthpiece of MIR Spirolab. Three consecutive readings were taken and the best reading amongst the three was selected.

PFT includes various lung volumes and lung capacities, of which we used 4 parameters of pulmonary function tests as follows

- **FEV1**-Maximum volume of air exhaled in first second of forced expiration from a position of full inspiration
- **FVC**-Forced vital capacity-the determination of vital capacity from a maximum forced expiratory effort
- **PEF**-Peak expiratory flow-the highest forced expiratory flow measured with a peak flow meter.
- **FEV1/FVC**

The pulmonary function of each subject was classified into four categories based on American Thoracic Society criteria as follows-

- **Normal**: FEV1, FVC within the normal range (at least 80% predicted) with FEV1/FVC at least 70%
- **Obstructive**: An FEV1/FVC ratio less than 70%, associated with decreased FEV1 and FVC (less than 80% predicted).
- **Restrictive:** Reduction in the FVC with a normal or elevated FEV1 -to-FVC ratio
- **Mixed obstructive and restrictive**: FEV1/FVC ratio reduced, suggestive of obstructive disease. Reduction in the FVC with abnormal or elevated FEV1 to-FVC ratio.

2.1 Statistical Analysis

Collected data was entered in MS-Excel 2007 and corrected for typographical errors and analyzed using SPSS 16.0 version. The comparison of qualitative data was done using chi square tests. The confidence limit for significance was fixed at 95% level with p-value <0.05.

3. Observations and Results

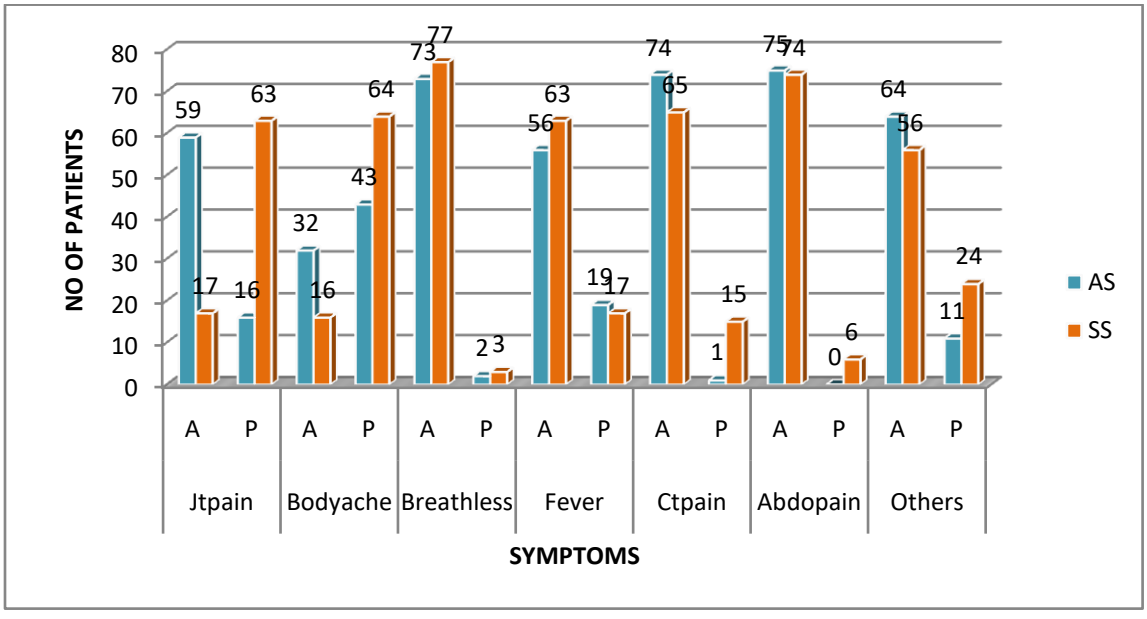
Total 155 patients of SCD were enrolled in the study, out of which 93 patients (60%) were male and 62 patients (40%) were females. Patients of sickle cell anemia (HBSS) were 80 (51.61%) while that of sickle cell trait (HBAS) was 75(48.38%). The majority of the patients in SS population were from the age group of 21-30 years [35 patients (43.80%)] and from AS population was from the age group 12-20 years [36 patients (48%)]. Mean age of the total population was 24.14±9.742 years. There was no statistically significant association between age group, area and sickle cell disease but statistically significant association observed between gender and sickle cell anemia as shown in table 1.

Table 1: Age, Gender and Area Wise Distribution of Patients

Distribution of Patients		HB Pattern			P-Value
		AS	SS	Total	
Age Wise	12-20	36 (48.00%)	31 (38.80%)	67 (43.20%)	0.086
	21-30	23 (30.70%)	35 (43.80%)	58 (37.40%)	
	31-40	8 (10.70%)	12 (15.00%)	20 (12.90%)	
	41-50	4 (5.30%)	2 (2.50%)	6 (3.90%)	
	>51	4 (5.30%)	0 (0.00%)	4 (2.60%)	
Sex Wise	Male	32 (42.70%)	61 (76.20%)	93 (60.00%)	0.00
	Female	43 (57.30%)	19 (23.80%)	62 (40.00%)	
Area Wise	Rural	33 (44.00%)	39 (48.80%)	72 (46.50%)	0.553
	Urban	42 (56.00%)	41 (51.20%)	83 (53.50%)	

The clinical presentation of patients was shown in figure 1. The most common symptom in both SS and AS was body ache and which found statistically significant association with sickle cell disease. In maximum number of patients' pallor was absent (72.9%) only 27.1% patients presented with pallor. Icterus was present in 18.1% patients and splenonegaly was also absent in majority of the patients (71.60%). There was statistical significant association between these signs and sickle cell disease.

Figure 1: Distribution of Patients According to Clinical Presentation



The mean hemoglobin level among total population was 9.03±1.721. The mean hemoglobin among SS population was 8.24 which was low as compared to AS population whose mean hemoglobin was 9.6. The distribution of patients according to HB and total serum bilirubin were shown in table 2.

Table 2: Distribution of Patients According to HB and Total Serum Bilirubin

Distribution of Patients		HB Pattern			P-Value
		AS	SS	Total	
Hemoglobin	<7	1 (1.30%)	16 (20.00%)	17 (11.00%)	0.00
	>7	74 (98.70%)	64 (80.00%)	138 (89.00%)	
Total Serum Bilirubin	Normal	75 (100.00%)	47 (58.80%)	122 (78.70%)	0.00
	Derranged	0 (0.00%)	33 (41.20%)	33 (21.30%)	

Most number of patients was having normal renal functions among total population (81.30%). There was no statistical significant association between EGFR and sickle cell disease, (p value 0.603). There were lower values of FEV1, FVC and PEFR among SS population as compared to AS population with increase in FEV1/FVC ratio (Table 3).

Table 3: Parameters of Pulmonary Function Tests

Parameters		HB Pattern			P-Value
		AS	SS	Total	
FEV1	>80	55(73.30%)	39 (48.80%)	94 (60.60%)	0.002
	<80	20 (26.70%)	41 (51.20%)	61(39.40%)	
FVC	>80	42 (56.00%)	25 (31.20%)	67 (43.20%)	0.006
	<80	33 (44.00%)	55 (68.70%)	88 (56.70%)	
FEV1/FVC	>70	73 (97.30%)	67 (83.80%)	140 (90.30%)	0.004
	<70	2 (2.70%)	13 (16.20%)	15 (9.70%)	
PEFR	>80	51 (68.00%)	35 (43.80%)	86 (55.50%)	0.002
	<80	24 (32.00%)	45 (56.20%)	69 (44.50%)	

The restrictive pattern of spirometry was more common among sickle cell patients (53.54%). Among SS population most common pattern was restrictive which was present in 62.50% patients while in AS population most common was normal spirometry followed by restrictive pattern (44%).

Among SS population in both male and female restrictive pattern was common, in male it was found in 36 patients (72%) and in females it was found in 14 patients (28%) while among AS population most common spirometry pattern was normal spirometry while second most common pattern was restrictive pattern which occurs

in 13 patients (39.40%) in males and 20 patients (60.60%) in females. We found no statistical significant association between age group and spirometry pattern in SS population, (p value 0.559) while found statistically significant association between spirometry pattern and AS population, (p value 0.025).

4. Discussion

Sickle hemoglobin is one of the most common and clinically significant structural abnormalities of hemoglobin, but no contemporary estimates exist of the global populations affected. Moreover, the precision of available national estimates of heterozygous (AS) and homozygous (SS) is unknown [8]. The present research was carried out with an objective to study and compare pulmonary function tests in patients with sickle cell trait and sickle cell anemia. All the selected patients were above 12 years of age which was similar to the study conducted by Mukuha, M Nyoro [9].

The maximum number of patients among SS population had lower FEV1 and FVC value as compared to AS population, this is similar to the study done by Achigbu *et al* [10]. Among SS population 67 patients (83.80%) had FEV1/FVC ratio >70% of predicted level. Among AS population 73 patients (97.30%) had FEV1/FVC >70% of predicted level. There was strong statistical significant association between FEV1/FVC and sickle cell disease, this finding is similar to the study done by Mukuha, M Nyoro [9]. SCA patients had an increased FEV1 to FVC ratio in keeping with a restrictive defect. The restrictive defect also showed significant negative relationship with number of crises and number of transfusions. Hence, SCA patients have predominantly a restrictive pattern of pulmonary dysfunction. Total 69 patients (44.50%) had PEFR <80% of predicted and 86 patients (55.50%) had PEFR >80% of predicted level. The present study did not included acute chest syndrome episodes among patients which differentiate this study from the previous study [11].

Pulmonary function tests was abnormal in 63.87% of total patients, among which most common abnormality was restrictive pattern which occurred in 83 patients (53.54%), obstructive pattern was present in 11 patients (7.09%) and mixed pattern in 5 patients(3.2%). These findings are comparable with the other studies [12, 13]. The authors of these studies had also done methacholine challenge test which was positive in 8 patients (31%) of sickle cell disease and 2 control subjects (7%). It has been suggested that there is a high prevalence of airway hyper responsiveness in adult patient with sickle cell anemia without history of airway disease. In current study we have excluded methacholine challenge test and also did not include TLC and RV but FEV1/FVC ratio was increased in 140 patients (90.30%) which suggests restrictive pattern.

Thus the current study found significant impairment of pulmonary function in sickle cell patients. Prior studies have suggested that abnormal pulmonary function tests are the first objective sign of chronic sickle cell lung disease and that they could be helpful in patient management [14]. Also, multiple small studies have demonstrated a spectrum of PFT abnormalities in adult sickle cell disease including restrictive physiology, decreased DlCO, hypoxemia, and obstructive disease [12, 15, 16]. The most common PFT abnormality observed was restrictive Disease as in current study as well as in others [12, 13, 16, 17].

Why in sickle cell patients abnormal pulmonary function is found even in asymptomatic period? In the sickle cell disease, mechanism of restriction would be ineffective inspiration due to chest wall pain related to peripheral vasoocclusion, prior rib infarctions, or vertebral disease [17]. Although the PFTs obtained in present study were done while the subjects were clinically at their baseline, even when clinically well, patients with Hb-SS may have ubacutevaso occlusion [18]. These entire factors may have contributed to chest wall discomfort during testing. As result of vasoocclusion, repeated bony infarction would have occurred during the growth and development, because of which there may be different chest wall structure [19]. Other cause for derangement in pulmonary function may be airway hyper responsiveness. The prevalence of airway hyper responsiveness was high in adult patients with sickle cell disease [13, 17].

Anti-inflammatory controller agents can be used routinely to decrease pulmonary morbidity associated with SCD, even in the absence of asthmatic symptoms [13, 17]. Younger age, serum IgE concentration, and LDH level, a marker of hemolysis, are associated with airway hyper responsiveness. Hemolysis and leukocytosis were independent risk factors for an early decline in lung volumes in this pediatric SCD cohort [20]. Other cause may be repeated episodes of acute chest syndrome may be a risk factor for development of pulmonary fibrosis a common etiology restrictive physiology [5]. Additionally this suggests that patient with restrictive lung disease have greater propensity toward vasoocclusion placing them at increased risk for development of bony infarcts. Development of pulmonary hypertension which occurs as result of chronic pulmonary crisis may also cause restrictive lung disease. Platelets appear to have an important role in the development of pulmonary hypertension, both as mediators of serotonin metabolism and in their role in thrombosis [16, 21]. In CT scan study in sickle disease patient, 41%had significant multifocal interstitial disease [12].

5. Conclusion

The chronic pulmonary complications in SCA are common. Abnormal pulmonary function was present in most of the patients (63.87%). Majority of patients of SS population were from the age group 21-30 years (43.75%) while most patients from AS population were from the age group of 12-20 years (48%), this may indicate decreased life span with age due to different complications in sickle cell disease. SCA patients have reduced FEV1 and FVC values, despite this reduction they had significantly increased FEV1/FVC ratio which is keeping a restrictive pattern of pulmonary dysfunction.

Limitation of the Study

We should have measured total lung capacity and diffusing capacity, as it was not possible for us as our sample size was large. In the future similar studies should be encouraged to assess all the parameters. In addition, testing for airway hyper reactivity, such as response to inhaled bronchodilators or methacholine challenge testing was not done. It is possible that subjects with coexistent asthma may not have been detected in the current study as airflow typically normalizes in these patients between acute exacerbations. We should have correlated pulmonary function abnormality with the haematological investigation which was not done in the present study, as our main aim was to assess the pulmonary function abnormality. In the future we would recommend further study where pulmonary function should be supplemented with radiological as well as haematological investigation.

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