

## Original Research Article

# Clinical profiling of sickle cell disease patients with respect to pulmonary hypertension

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### ABSTRACT

**Background:** Sickle cell disease (SCD) is the commonest heritable hematologic abnormality affecting humans. Pulmonary hypertension is documented in patients of SCD by both non-invasive methods and catheterization, with incidence reported to be as high as 20%-63%. However, pulmonary hypertension has not been studied as complication of patients of sickle cell disease in India.

**Methods:** A total of 94 (54 SS and 40 AS) more than 12 years old cases diagnosed to have sickle cell disease by hemoglobin electrophoresis were recruited. All the participants were assessed with complete history, general and systemic examination, hematological and biochemical tests, X-ray chest, ECG, pulmonary function tests and 2D echocardiography and Doppler studies. Cases were observed in 2 groups: SS cases and AS cases. Sixty four age/sex matched healthy close relatives of the cases with 'AA' Hb electrophoresis pattern were the controls.

**Results:** Five SS cases were detected to have pulmonary hypertension. Pulmonary hypertension was not detected in any AS case or control. Pulmonary hypertension was more common in females (3/23, 13%) than males (2/26, 7.7%). The mean age of the SS cases with PH (32±5.15) was found to be significantly higher than that of the SS cases without PH (24.2±6.21) (p<0.01).

**Conclusions:** The incidence of PH was low in this study, as compared to western studies. This may be since most of the cases of SCD being in remote areas having no access to health care facilities.

**Keywords:** Sickle cell disease, Pulmonary hypertension

### INTRODUCTION

Sickle cell disease is the commonest heritable hematologic abnormality affecting humans.<sup>1</sup> The average incidence of sickle gene among Indians is approximately 4.3%.<sup>2</sup> The frequency is much higher (up to 45%) in many tribal population in India.<sup>3</sup> The prevalence of sickle cell disease is higher in central India and certain localities of Maharashtra.<sup>4</sup>

Pulmonary hypertension (PH) is one of the serious complications of sickle cell disease.<sup>5</sup> Various etiological

factors have been promulgated are recurrent in-situ thrombosis, thromboembolism, increased blood viscosity, repeated infections, fat embolism and passive rise in pressure due to chronic anaemia.<sup>6-8</sup> Pulmonary hypertension has been well documented in patients of sickle cell disease by both non-invasive methods (2D echo and Doppler studies) as well as by catheterization. The incidence has been reported to be as high as 20%-63%.<sup>8-10</sup> However, pulmonary hypertension has not been studied as complication of patients of sickle cell disease in India. The present study was therefore conducted to study the clinical profile of cases of sickle cell disease

attending the hospital and to evaluate them for pulmonary hypertension by Doppler and echocardiography.

## METHODS

### Study type

Hospital based prevalence study.

### Study period

May 2002 to November 2003, one and half year

### Study setting

Department of Medicine, tertiary care government hospital, Central India.

### Inclusion criteria

Inclusion criteria were age more than 12 years old; diagnosed to have sickle cell disease by hemoglobin electrophoresis

### Exclusion criteria

Exclusion criteria were sickle cell disease patients with cardiovascular diseases and history of smoking, history / evidence of lung diseases; pulmonary hypertension due to other causes.

Cases enrolled as per mentioned selection criteria were screened by complete history, general examination, systemic examination, hematological and biochemical tests, X-ray chest, ECG, pulmonary function tests and 2Dechocardiography and Doppler studies. 2Dechocardiography and Doppler studies were performed in the crisis free period. The cases were observed in 2 groups: SS cases and AS cases. Sixty four age and sex matched healthy close relatives of the cases, who had 'AA' Hb electrophoresis pattern were the study controls.

The cases and controls were subjected to the following hematological investigations:

- Hb in gram% by Sahli's hemoglobinometer
- Sickling by slide test using sodium metabisulphite
- Hb electrophoresis by the cellulose acetate method at alkaline pH
- Peripheral smear
- Reticulocyte count

### Operational definitions

- On clinical examination, pulmonary hypertension was suspected by the presence of parasternal heave, loud or palpable P<sub>2</sub> and/or ejection systolic murmur in the left parasternal area.<sup>11</sup>

- On ECG evaluation, pulmonary hypertension was diagnosed by P pulmonale and right ventricular hypertrophy (R in V<sub>1</sub> > 5 mm or R/S in V<sub>1</sub> ≥ 1 or R/S in V<sub>5,6</sub> < 1) and/or mean QRS axis ≥ +110°.<sup>11,12</sup>
- On X-ray chest examination, pulmonary hypertension was diagnosed by:<sup>13</sup>
  - Prominent pulmonary conus
  - Increased width of the right descending pulmonary artery, >15 mm in females and 16mm in males
  - Peripheral oligoemia i.e. decrease in the size of the peripheral vessels within 2 cms of the pleura.
- Cardiomegaly- Cardio-thoracic ratio >0.5 in X-ray chest postero-anterior view taken in standing position in full inspiration.

Data was analysed using SPSS (version 20) and expressed as mean±standard deviation. Non continuous variables were analysed using the chi square test while continuous variables were analysed using the unpaired student's t-test.

Approval was obtained from the Institutional Ethics Committee before starting the study. Written informed consent were elicited from all the participants.

## RESULTS

In the present study a total of 94 (54 SS and 40 AS) cases were recruited. 64 age and sex matched controls were also studied. Of the 54 SS cases, 28 (51.9%) were males and 26 (48.1%) were females. Of the 40 AS cases, 18 (45%) were males and 22 (55%) were females. Of the 64 controls 32 (50%) each were males and females. Maximum number of cases, i.e. 44 (46.8%) out of 94 were in the age group 21-30. This included 28 (51.8%) SS and 16 (40%) AS cases.

Five SS cases were detected to have pulmonary hypertension. Pulmonary hypertension was not detected in any AS case or control. Pulmonary hypertension was more common in females (3/23, 13%) than males (2/26, 7.7%).

The mean age of the SS cases with PH (32±5.15) was found to be significantly higher than that of the SS cases without PH (24.2±6.21) (p<0.01). No significant difference was observed in the mean age between the SS and the AS cases.

Significant number of cases belonged to the Mahar caste, 36 (66.7%) SS and 29 (72.5%) AS, as compared to the rest of the castes individually or altogether. Four cases of PH were reported from Mahar caste while one belonged to Gond caste.

When inquiry was made for symptoms amongst participants; the most common complaint was pain in extremities present in 50 (92.6%) SS and 18 (45%) AS cases followed by pain in joints present in 48 (88.9%) SS

and 16 (40%) AS cases. Jaundice was present in 42 (77.8%) SS and 8 (20%) AS cases. Chest pain was present in 16 (29.6%) SS and 7 (17.5%) AS cases. Cardiac symptoms: palpitations and dyspnoea were present in 25 (46.3%) and 17 (31.5%) SS cases and 8 (20%) and 2 (5%) AS cases respectively. When the incidences of cardiac symptoms (palpitations and dyspnoea), pain in extremities, pain in joints and jaundice were compared between the SS and AS cases, the incidences were found to be significantly high ( $p < 0.01$ )

in the SS cases. However, there were no significant differences in the incidences of chest pain, pain in abdomen, fever and cough when compared between these two groups. When the incidences of the above symptoms were compared between the SS cases, with and without PH, the incidence of dyspnoea was found to be significantly high ( $p < 0.01$ ) in the SS cases with PH. No significant difference was found in the incidences of any other symptom between these two groups (Table 1).

**Table 1: Distribution of symptoms & clinical profile amongst cases and controls.**

	SS cases			AS cases (n=40) (%)	Controls (n=64) (%)
	With PH (n=5) (%)	Without PH (n=49) (%)	Total (n=54) (%)		
<b>Symptoms</b>					
Pain in extremities	5 (100)	45 (91.8)	50 (92.6)	18 (45)	0
Pain in joints	5 (100)	43 (87.8)	48 (88.9)	16 (40)	0
Jaundice	5 (100)	37 (75.5)	42 (77.8)	8 (20)	0
Palpitations	3 (60)	22 (44.9)	25 (46.3)	8 (20)	0
Chest Pain	3 (60)	13 (26.5)	16 (29.6)	7 (17.5)	0
Dyspnea	5 (100)	12 (24.5)	17 (31.5)	2 (5)	0
Pain in abdomen	2 (40)	12 (24.5)	14 (25.5)	5 (12.5)	0
Fever	2 (40)	7 (14.3)	9 (16.7)	3 (7.5)	0
Cough	1 (20)	3 (6.1)	4 (7.4)	3 (7.5)	0
<b>VOC/year</b>					
0	0	0	0	16 (40)	0
1-6	1 (20)	40 (81.6)	41 (75.9)	23 (57.5)	0
>6	4 (80)	9 (18.4)	13 (24.1)	1 (2.5)	0
<b>B.T.s/year</b>					
0	0	21 (42.8)	21 (38.9)	34 (85)	0
1-2	1 (20)	24 (49)	25 (46.3)	6 (15)	0
>2	4 (80)	4 (8.2)	8 (14.8)	0	0
<b>Hospitalizations/year</b>					
0	0	17 (34.7)	17 (31.5)	29 (72.5)	0
1-3	1 (20)	24 (49)	25 (46.3)	10 (25)	0
>3	4 (80)	8 (16.3)	12 (22.2)	1 (2.5)	0

\*in last 5 years, on history; VOC: Vaso-Occlusive Crisis; B.T.: Blood Transfusion

When history of last 5 years was considered for number of vaso-occlusive crises (VOC), blood transfusion (BTs) received and the need for hospitalization; a past history of VOC was found in all 54 (100%) SS and 24 (60%) AS cases. Of these, 13 (24.1%) SS cases and 1 (2.5%) AS case had a frequency of >6 episodes per year. Thirty three (61.1%) SS cases and 6 (15%) AS cases had received BTs. Of these, 8 (14.8%) SS cases had received an average of >2 units per year (Table 1).

History of hospitalization was present in 37 (68.5%) SS and 11 (27.5%) AS cases. Of these, 12 (22.2%) SS and 1 (2.5%) AS case had an average frequency of >3 hospitalizations per year, in the last five years. When the SS and the AS cases were compared for history of VOC >6/year, number of BTs >2/year and number of

hospitalizations >3/year, the SS cases were found to have significantly high ( $p < 0.01$  each) incidences of the above 3 parameters vs. the AS cases. The incidence of the above 3 parameters was also found to be significantly high ( $p < 0.01$ ) in the SS cases with PH vs. the SS cases without PH. (Table 1)

As for signs amongst study participants; Pallor was present in 51 (94.4%) SS and 24 (60%) AS cases, hemolytic facies in 51 (94.4%) SS and 3 (7.5%) AS cases and icterus in 35 (64.8%) SS and 6 (15%) AS cases. Tachycardia, tachypnoea and signs of CCF were present in 8 (14.8%), 7 (13%) and 6 (11.1%) SS and 3 (7.5%), 1 (2.5%) and 0 AS cases respectively. Fever was present in 6 (11.1%) SS and 3 (7.5%) AS cases. When the SS and AS cases were compared for the incidences of the above

signs, the SS cases were found to have significantly higher incidences of pallor, hemolytic facies, icterus, ( $p < 0.01$  each), and signs of CCF ( $p < 0.05$ ). When the SS cases with and without PH were compared for the above

signs, the incidences of tachycardia and tachypnoea were found to be significantly higher in the SS cases with PH ( $p < 0.05$ ) (Table 2).

**Table 2: Distribution of physical signs amongst cases and controls.**

Signs	SS cases			AS Cases (n=40) (%)	Control (n=64) (%)
	With PH (n=5) (%)	Without PH (n=49) (%)	Total (n=54) (%)		
<b>Pallor</b>	5 (100)	46 (94)	51 (94.4)	24 (60)	13 (20.3)
<b>Hemolytic facies</b>	5 (100)	46 (94)	51 (94.4)	3 (7.5)	0
<b>Icterus</b>	5 (100)	30 (61.2)	35 (64.8)	6 (15)	0
<b>Tachycardia</b>	3 (60)	5 (10.2)	8 (14.8)	3 (7.5)	0
<b>Tachypnoea</b>	3 (60)	4 (8.2)	7 (13)	1 (2.5)	0
<b>Signs of CCF</b>	2 (40)	4 (8.2)	6 (11.1)	0	0
<b>Fever</b>	1 (20)	5 (10.2)	6 (11.1)	3 (7.5)	0

**Table 3: Distribution of findings of systemic examination in the study.**

	SS Cases			AS Cases (n=40) (%)	Control (n=64) (%)
	With PH (n=5) (%)	Without PH (n=49) (%)	Total (n=54) (%)		
<b>Cardiovascular system</b>					
PSH*	3 (60)	0	3 (5.6)	0	0
Palpable P <sub>2</sub>	3 (60)	0	3 (5.6)	0	0
Loud P <sub>2</sub>	3 (60)	0	3 (5.6)	0	0
SSM*	5 (100)	15 (30.6)	20 (37)	4 (10)	0
<b>Respiratory system</b>					
Crepitations	3 (60)	3 (6.1)	6 (11.1)	0	0
<b>Abdomen</b>					
Liver	2 (40)	9 (18.4)	11 (20.4)	3 (7.5)	0
Spleen	2 (40)	9 (18.4)	11 (20.4)	2 (5)	0
<b>Musculoskeletal system</b>					
AVN* femur head	2 (40)	4 (8.2)	6 (11.1)	0	0
AVN* humerus head	1 (20)	0	1 (1.8)	0	0
<b>Renal involvement</b>					
Renal involvement	2 (40)	5 (10.2)	7 (13)	0	0
Cholelithiasis (USG)	3 (60)	3 (6.1)	6 (11.1)	1 (2.5)	0
<b>Central nervous system</b>					
Epistaxis	1 (20)	0	1 (1.8)	0	0

\*PSH- parasternal heave, SSM- soft systolic murmur, AVN- Avascular necrosis.

When the SS cases were compared with the AS cases for the findings of systemic examination, the SS cases were found to have significantly higher incidences of soft systolic murmur ( $p < 0.01$ ), crepitation ( $p < 0.05$ ), palpable spleen ( $p < 0.05$ ), avascular necrosis of bone ( $p < 0.05$ ) and renal involvement ( $p < 0.05$ ). When SS cases were considered, with and without PH, on CVS examination, SSM was present in 5 (100%) SS cases with PH and 15 (30.6%) SS cases without PH. Clinical diagnostic signs of PH (PSH, palpable and loud P<sub>2</sub>) were detected in only 3 (60%) SS cases out of total 5 cases diagnosed to have PH on Doppler.

When other findings of systemic examination were considered, 3 (60%) SS cases with PH and 3 (6.1%) SS cases without PH had crepitation. 2 (40%) SS cases with PH and 9 (18.4%) SS cases without PH had a palpable liver and a palpable spleen, each. 3 (60%) SS cases with PH had avascular necrosis of bone (2-femur head and 1-humeral head) while 4 (8.2%) SS cases without PH had avascular necrosis of the femur head. 2 (40%) SS cases with PH and 5 (10.2%) SS cases without PH had renal involvement. 3 (60%) SS cases with PH and 3 (6.1%) without PH had gallstones. The SS cases with PH were found to have significantly higher incidences of PSH, palpable P<sub>2</sub>, loud P<sub>2</sub>, soft systolic murmur, crepitations

( $p < 0.01$  each), avascular necrosis of bone ( $p < 0.05$ ) and cholelithiasis ( $p < 0.05$ ) (Table 3).

The SS cases had significantly low mean Hb level and significantly high reticulocyte count and serum bilirubin vs. the AS cases as well as vs. the controls ( $p < 0.01$  each). The AS cases also had significantly low mean Hb level and significantly high reticulocyte count and serum bilirubin vs. the controls ( $p < 0.01$  each). There were no significant differences in the above values when compared between the SS cases, with and without PH.

When the SS and AS cases were compared for incidence of severe anemia with Hb level  $\leq 7$  gram%, SS cases were found to have significantly greater incidence ( $p < 0.05$ ). However, no significant difference was found between the SS cases, with and without PH in the incidence of severe anemia. The SS cases had a significantly higher incidence of serum bilirubin level above 4 mg% when compared vs. the AS cases ( $p < 0.01$ ). There was no significant difference in the incidence of serum bilirubin level above 4 mg% between the SS cases, with and without PH.

In the present study, 11 (20.4%) SS and 2 (5%) AS cases had cardiomegaly. When signs of PH on X-ray chest were considered, 3 (5.6%) SS cases had a dilated right descending pulmonary artery and out of these 3 cases, 2 (3.7%) cases also had prominent pulmonary conus. No case in the study had peripheral oligoemia. 6 (11.1%) SS cases in the study had infiltrates on X-ray chest, which are evidence of infection or infarction. 4 (7.4%) SS cases had basal septal lines due to pulmonary congestion. Of the 5 SS cases with PH, 3 (60%) cases had cardiomegaly and 2 (40%) each had infiltrates and basal septal lines.

4 (7.5%) SS cases had ST-T changes in the form of ST-T straightening or T inversion in the anterior leads. 7 (13%) SS cases had LVH. When evaluated for signs of PH on ECG, 2 (3.7%) SS cases had these signs (1 case had sinus tachycardia, RAD and RVH, while the other had sinus tachycardia, P pulmonale, RAD and RVH). Of the other 3 cases detected to have PH on Doppler echocardiography, 1 had sinus tachycardia and LVH, 1 had LVH and ST-T changes and the other had a normal ECG.

In the study, 11 (20.4%) SS and 3 (7.5%) AS cases had abnormal ventilatory patterns. Of the 11 SS cases, 6 (11.1%) had a mild restrictive defect and 5 (9.3%) had a mixed defect. The 3 AS cases had a mild restrictive defect. When the 5 SS cases with PH were considered, 2 (40%) had mild restrictive defects, 1 (20%) had a mixed defect and 2 (40%) cases had normal PFTs. No case in the study had a pure obstructive defect. The SS cases had significantly greater mean LA ( $p < 0.05$ ) and mean LV ( $p < 0.01$ ) dimensions vs. the AS cases, as well as the controls. The AS cases had significantly greater LV dimensions vs. the controls ( $p < 0.01$ ). In the study, when the SS cases, with and without PH were compared, the SS cases with PH had significantly greater mean LV and RV

dimensions ( $p < 0.01$  each) vs. the SS cases without PH. In the study, 8 (15%) SS cases had a dilated LV and 2 (3.7%) had a dilated RV. None of the AS cases had any dilated chamber. Of the 5 cases with PH, 3 (60%) had a dilated LV and 2 (40%) of these 3 cases had an associated dilated RV. When the SS and AS cases were compared for the incidences of dilated LV and RV, the incidence of dilated LV was found to be significantly higher in the SS cases ( $p < 0.05$ ). When the SS cases, with and without PH were compared, the SS cases with PH were found to have significantly high incidences,  $p < 0.05$  and  $p < 0.01$ , of dilated LV and RV respectively.

## DISCUSSION

Out of these 94 total cases and 64 controls, 5 SS cases were detected to have pulmonary hypertension. Pulmonary hypertension was not detected in any AS case or control.

In the present study, we did not get any male preponderance. Kar also found no specific sex predilection in his study of 636 SS cases.<sup>14</sup> In our study, maximum cases were in the age group 21-30 years in both SS and AS cases (28 SS and 16 AS). This is in accordance with the studies of Kar et al and other similar studies.<sup>15</sup> The mean age of patients of SS disease, with PH was 32 years and without PH was 24.2 years. The difference was statistically significant ( $p < 0.01$ ). Sutton et al also found that the mean age of patients with PH tended to be higher but the difference was not statistically significant.<sup>8</sup> In our study, maximum number of cases were from the Mahar caste; I fact well established previously.

In our study, the commonest symptoms were pain in extremities and joints found in 50 (92.6%) and 48 (88.9%) SS cases and 18 (45%) and 16 (40%) AS cases, respectively. The incidence in SS cases in the present study is similar to that found by Kar et al, Kaur et al and Abhyankar et al, amongst others.<sup>15-17</sup>

In our study, when the incidences of the cardiac symptoms (palpitations and dyspnea) were compared between the SS cases with and without PH, the incidence of dyspnea was found to be significantly high ( $p < 0.01$ ) in the SS cases with PH. No significant differences were found in the incidences of other symptoms between these two groups. Sutton et al<sup>8</sup> found cardiac symptoms in 7/12 (58%) SS cases with PH, and in only 13/48 (27%) SS cases without PH,  $p = 0.04$ . This correlates with our study for dyspnea.

The phenotypic expression of sickle cell anemia in India is not uniformly mild. Different population groups show varying severity of clinical manifestations. The present study was a local one and wider studies covering different population groups are needed to compute the incidence of PH in Indian sicklers.

The decreased incidence may also be due to increased mortality in cases with PH who were not diagnosed in the remote areas or did not have access to health care facilities. Many populations with SCD are economically worse off, with poor nutritional and low Hb status, low earning capacity and poor access to health care facilities<sup>16</sup>. And this study is based on a population which is attending an urban medical college hospital.

Non-invasive tests like X-ray chest, ECG and Doppler echocardiography may not demonstrate early and/ or every evidence of PH.<sup>17</sup> Right-sided cardiac catheterization remains the only gold standard to detect PH.<sup>18</sup> Some cases in the present study may have had mild PH, which could not be detected by Doppler and echocardiography. However, in our opinion, cardiac catheterization studies in these patients are unjustified for the diagnosis of PH, since it does not seem to help in management nor it helps in altering the prognosis of these patients and also the ethical committee would not permit it.

Cardiac catheterization may be used to establish the severity of PH and to assess the prognosis.<sup>11</sup> It can be used to establish baseline pulmonary hemodynamics prior to treatment. Vasodilators like nitric oxide and prostacyclin have shown definite benefit in conditions like primary pulmonary hypertension, neonatal pulmonary hypertension and the adult respiratory distress syndrome.<sup>11</sup> However, their benefit in PH associated with sickle cell disease is yet to be established. Trials are underway to test the efficacy of nitric oxide and arginine in PH associated with sickle cell disease. Definitive benefit is not yet established. Till clear advantage is proved, the use of vasodilators in the treatment of PH in sickle cell disease remains experimental.

The present study was an urban hospital based study. The sample size was relatively small. Therefore, our results may not be applicable to patients in the community. Information based on a clinical sample could be distorted and variable depending on the referral pattern and disease pattern in the locality. Wider prospectively carried out population based studies are needed to compute the incidence of PH in cases of SCD.

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