

Prevalence of Pulmonary Hypertension in Children with Sickle Cell Disease

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Abstract: **Background:** To determine the prevalence of elevated pulmonary artery pressures and associated risk factors in children with sickle cell disease. **Methods:** A descriptive and cross sectional observational study was done over the period of 09 months. All patients between the age group of 5 to 18 years diagnosed to have Sickle Cell Syndromes were included. A complete physical examination was performed and the details of patient's age, age at diagnosis, age at first transfusion, frequency of transfusion, history of sickling crisis including the type and number of crisis were analyzed. Investigations done were complete hemogram with reticulocyte count, liver function tests, renal function tests, chest radiograph, electrocardiogram and a 2D echocardiogram. Quantitative data was analyzed by proportion and Chi square test. **Results:** Total 50 patients (30 males, 20 females) were enrolled in the study between the age group of 5 - 18 years with the mean age 11.3 ± 3.7 years. Overall prevalence of pulmonary hypertension (PHT) was 38%. Mild PHT (TR Jet velocity 2.5 to 2.9m/second) was found in 12 (24%) patients, 7 (14%) patients had moderate to severe PHT (TR jet velocity >3 m/second). Elevated tricuspid regurgitant jet velocity was more in patients with Hb - SS disease (38.6%) as compared Hb - S/ β + thalassemia (36.6%). A high reticulocyte count ($p=0.036$), low hemoglobin ($p=0.046$), increased number of crisis ($p=0.048$), more frequent packed red cell transfusions ($p=0.043$), high LDH ($p=0.045$) and a high bilirubin levels ($p=0.041$) were significantly associated with elevated pulmonary artery pressures. There was no difference in age of presentation, gender, age of first packed red cell transfusion between patients with and without elevated PHT. **Conclusions:** High pulmonary artery pressures do occur in children with sickle cell disease. Screening by echocardiography can lead to early detection and intervention.

Keywords: SCD, sickle cell disease, hemoglobinopathies

1. Introduction

Sickle cell disease (SCD) is a congenital structural haemoglobinopathy, inherited in an autosomal recessive manner. It is caused by a single point mutation in the β - globin gene that changes the sixth amino acid from glutamic acid to valine. Sickle cell anemia includes both homozygous SS and heterozygous AS state.¹ Sickle cell anemia, though rare in India, with prevalence of heterozygotes varying from 1 - 40 per cent occurs in wide geographical distribution from Orissa, Maharashtra, Madhya Pradesh and Jharkhand.²

Pulmonary hypertension (PHT) may develop in most forms of hereditary and chronic haemolytic anemia during intravascular haemolysis including sickle cell anemia, thalassemia, hereditary spherocytosis and paroxysmal nocturnal haemoglobinuria.³ Cross - sectional studies have found associations between the degree of haemolysis and marker of pulmonary artery pressure in individual with sickle cell anemia. Elevated tricuspid regurgitation velocity (TRV) and left ventricular diastolic dysfunction develop in children with sickle cell anemia, but the clinical importance is unclear. In particular, whether screening and intervention for these complications should begin in childhood is not known. In the few longitudinal studies of cardiopulmonary complication in children with sickle cell anemia that have been reported but its association with mortality during the short duration of follow up has not been observed.⁴ PHT occurs in 32% of adults with sickle cell anemia and is associated with an increased risk of mortality.⁵ There is limited data on the prevalence of pulmonary hypertension in

children with sickle cell anemia. Recent studies have found the prevalence of pulmonary hypertension in children to be between 16% and 26.2 %.⁶ We undertook this study to determine the prevalence of PHT in patients with SCD in our population.

2. Methods

This is a descriptive and a cross sectional Observation study which was carried over a period of 9 months from February 2022 – November 2022 at SVNGMC, Yavatmal Maharashtra, India.

Total 50 patients diagnosed as sickle cell syndromes who attended the outdoor services were selected on random basis.

Inclusion criteria

All patients between the ages of 5 to 18 years diagnosed to have Sickle Cell Syndromes on HPLC, including homozygous i.e. HbSS and double heterozygous state i.e. Hb - SC, Hb - SD, Hb - S/ β +, Hb - S/ β 0 who were registered at our centre for regular treatment were included in the study.

Exclusion criteria

Patients with pulmonary stenosis/or any other structural obstruction to pulmonary blood flow were excluded.

3. Methodology

A detailed history of each patient was taken with special reference to the patient's age, age at diagnosis, age at first

transfusion, frequency of transfusion, history of sickling crisis including the type and number of crisis and was noted in a predesigned proforma. A complete physical examination was performed and findings were noted. Special emphasis was laid on the presence of anemia, icterus, heptoslenomegaly and stigmata of sickle cell crisis. All children were administered standard care including penicillin prophylaxis, vaccination for encapsulated organisms, zinc and hydroxyurea (HU) if indicated.7 Detailed treatment history of hydroxyurea, including age of starting HU, dose at initiation and at maintenance as well as any toxicity related to drug causing discontinuation were noted. All patients in the study group received hydroxyurea in the range of 15 to 25 mg/kg/day for an average of one to five 5 years of duration. Investigations done in all patients were complete hemogram with reticulocyte count, liver function tests, renal function tests with lactate dehydrogenase (LDH), chest radiograph, electrocardiogram and a 2D echocardiography. A vivid I GE7 Two - dimensional Doppler echocardiography was performed for all patients. Transthoracic transducer selection was made for echocardiographic window as per every patient. Cardiac measurements were performed according to the guidelines of American Society of Echocardiography.8 TRV was measured by pulsed - wave and continuous wave Doppler echocardiography wherever applicable. Multiple views (apical 4 - chamber, parasternal short axis, parasternal long axis) were obtained to record optimal tricuspid Doppler flow signals, and a minimum of 5 sequential signals were recorded. The right ventricular to right atrial systolic pressure gradient was calculated using the modified Bernoulli equation ($4 \times V2$). Pulmonary artery systolic pressure was quantified by adding the Bernoulli - derived right ventricular systolic peak pressure to the estimated mean right atrial pressure (5 mm Hg). Pulmonary artery diastolic pressure was estimated by measurement of the end diastolic velocity of the pulmonary insufficiency jet by similar Doppler techniques. Pulmonary hypertension was defined as a peak TRV of at least 2.5 m/second equating to a pulmonary artery pressure of at least 30 mm Hg. Mild pulmonary hypertension was defined as peak TRV of 2.5 to 2.9 m/second, corresponding to pulmonary artery systolic pressure of 30 to 39 mm Hg. Moderate pulmonary hypertension was defined as a peak TRV ≥ 3 m/second corresponding to pulmonary artery systolic pressure of 40 to 70 mm Hg and severe pulmonary hypertension was corresponding to pulmonary artery systolic pressure of >70 mm Hg. Patients with no measurable TRV or TRV <2.5 m/second were considered to have normal pulmonary artery pressures and normal tricuspid flow 0.6 (0.5–0.8) in children.

Statistical analysis

All results were analysed using SPSS software version 20. Quantitative variable has been presented by mean + standard deviation. Quantitative data was analysed by proportion and Chi square test at $p < 0.05$ level of significance.

4. Results

A total of 50 patients (30 males and 20 females) with sickle cell disease were enrolled in the present study with male to

female sex ratio of 3: 2. Overall prevalence of pulmonary hypertension in the study group was 38% (19/50). Of these, 12 (24%) patients had mild pulmonary hypertension, 7 (14%) patients had moderate pulmonary hypertension and, 31 (62%) patients had normal pulmonary pressures (Figure 1).

Table 1: Correlation of prevalence of PHT in various age groups

		PHT			Total
		Mild	Moderate	Normal	
Age (Years)	5 to 10	4	3	14	21
		19.0%	14.3%	66.7%	100.0%
	11 to 15	8	4	12	24
		33.3%	16.7%	50.0%	100.0%
	15 - 18	0	0	5	5
	0.0%	0.0%	100.0%	100.0%	
Total		12	7	31	50

In demographic details, 21 patients (42%) belonged to the age group of 5 to 10 years, 24 (48%) were between 11 to 15 years and 5 (10%) were in the age group of 15 to 18 years with the mean age 11.3 ± 3.7 years. Maximum patients who developed pulmonary hypertension were in the age group of 11 to 15 years (Table 1).

Table 2: Correlation of prevalence of PHT with types of sickle cell disease

	PHT			Total
	Mild	Moderate	Normal	
Sickle cell homozygous	8	2	16	26
	30.8%	7.7%	61.5%	100.0%
HbS/D disease	1	0	1	2
	50.0%	0.0%	50.0%	100.0%
HbS/ β + thalassemia	3	5	14	22
	13.6%	22.7%	63.6%	100.0%
Total	12	7	31	50
	24.0%	14.0%	62.0%	100.0%

P value: 0.365

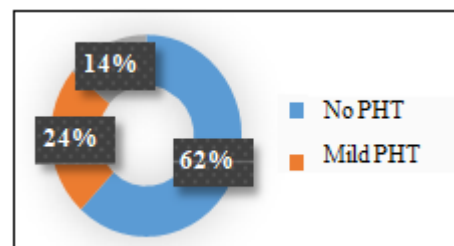


Figure 1: Grades of pulmonary hypertension in sickle cell disease.

Of the total 50 patients, 26 (52%) were diagnosed as sickle cell homozygous, 22 (44%) were S/ β Thalassemia and only 2 (4%) patient were diagnosed as sickle HBSD disease. As shown in Table 2, Elevated tricuspid regurgitant jet velocity was more in patients with Hb - SS disease (38.6%) as compared Hb - S/ β + thalassemia (36.6%) though it was statically not significant. ($p=0.365$). Children with Sickle cell disease and pulmonary hypertension presented with symptoms of crisis at an earlier age 4.1 ± 3.11 years as compared to those with normal pulmonary hypertension 5.4 ± 2.91 years which was statistically significant ($P=0.041$).

Table 3: Correlation of crisis with PHT

Types of crisis	PHT			Total
	Mild	Moderate	Normal	
Bony crises (VO)	8	4	24	36
No Crisis	1	1	2	4
Vo+Hemolytic	2	0	2	4
Acute Chest Syndrome	0	2	0	2
Sickle hepatopathy	0	0	2	2
Hemolytic	1	0	0	1
Splenic sequestration	0	0	1	1
Total	12 (24%)	7 (14%)	31 (62%)	50 (100%)

Table 4: Association of various factors with PHT

	PHT	N	Mean	SD	SE of mean	T value	P value	Significance
Age at diagnosis	No	31	5.8065	2.99354	0.53766	0.261	0.795	No
	Yes	19	5.5789	2.98730	0.68533			
Age at first symptom	No	31	5.4839	2.91971	0.52440	2.374	0.041	Yes
	Yes	19	4.1579	3.11383	0.71436			
Age of 1st transfusions	No	31	4.8065	3.48730	0.62634	0.47	0.641	No
	Yes	19	5.2632	3.07033	0.70438			
No. of PRC transfusion	No	31	3.4516	7.04196	1.26477	2.231	0.043	Yes
	Yes	19	6.1579	8.31507	1.90761			
Age of starting HU years	No	31	6.9677	3.84260	0.69015	1.943	0.049	Yes
	Yes	19	6.0000	2.90593	0.66667			
HU mean dose	No	31	19.7419	4.93266	0.88593	2.108	0.045	Yes
	Yes	19	20.5789	5.55093	1.27347			
Weight kg	No	31	27.2258	10.02234	1.80007	1.029	0.308	No
	Yes	19	30.2105	9.83519	2.25635			
Hb Baseline	No	31	7.2581	1.76951	0.31781	1.993	0.046	Yes
	Yes	19	6.3158	2.60454	0.59752			
MCV baseline	No	31	72.2581	9.93971	1.78522	2.306	0.043	Yes
	Yes	19	76.1053	10.39709	2.38526			
MCV after HU	No	31	85.7742	13.19270	2.36948	0.161	0.873	No
	Yes	19	85.2105	9.70440	2.22634			
Retic count baseline	No	31	3.4516	1.17866	0.21169	2.156	0.036	Yes
	Yes	19	4.4211	2.00875	0.46084			
Hb on treatments	No	31	9.5806	1.76587	0.31716	0.686	0.496	No
	Yes	19	9.2632	1.24017	0.28451			
Retic at presentation	No	31	2.9355	2.09659	0.37656	0.554	0.582	No
	Yes	19	2.6316	1.46099	0.33517			
Total bilirubin	No	31	1.5806	1.31083	0.23543	2.383	0.041	Yes
	Yes	19	2.4211	1.60955	0.36926			
Indirect bilirubin	No	31	0.8710	1.14723	0.20605	2.303	0.045	Yes
	Yes	19	1.7368	1.28418	0.29461			
Hemolytic episodes	No	31	0.0968	0.30054	0.05398	1.875	0.049	Yes
	Yes	19	0.4737	1.61136	0.36967			
No. of crisis in lifetime	No	31	1.2903	1.24348	0.22334	1.965	0.048	Yes
	Yes	19	2.4737	2.96963	0.68128			
Serum LDH	No	31	996.7742	374.87035	67.32870	2.127	0.045	Yes
	Yes	19	885.7895	265.21429	60.84433			
No of VO crisis	No	31	1.3548	0.984	0.17495	2.130	0.046	Yes
	Yes	19	1.7368	1.77375	0.40693			

Though sickle cell disease is an autosomal recessive, only 4 (8%) patients in the study group were born out of 3rd degree consanguineous marriage. 27/50 (54%) belonged to Bouddha community and 23/50 (46%) patients were of different tribal communities of Maharashtra.

In this study group, patients who faced frequent sickle cell crises developed pulmonary hypertension as compared to those with less or no sickle crises (p=0.048) (Table 3). Patients who had raised biochemical markers of haemolysis at presentation had statistically significant rise in pulmonary hypertension. A high reticulocyte count (p=0.036), low hemoglobin (p=0.046), increased number of crisis

(p=0.048), more frequent packed red cell transfusions (p=0.043), high LDH (p=0.045) and a high bilirubin levels (p=0.041) were significantly associated with elevated pulmonary artery pressures. There was no difference in gender, age of presentation, age of first packed red cell transfusion between patients with and without elevated PHT (Table 4).

On comparing the difference in hemoglobin levels at baseline and post hydroxyurea, the response to hydroxyurea for rise in hemoglobin from baseline was significantly less in patients with pulmonary hypertension (p=0.04). When association with organomegaly was studied, patients with

pulmonary hypertension had clinically significant larger liver and spleen, compared to patients not having pulmonary hypertension, but the statistical correlation was poor ($p=0.8571$, $p=0.194$ respectively).

5. Discussion

Intravascular haemolysis leading to nitric oxide deficiency is hypothesized as a major pathogenic mechanism for pulmonary hypertension in Sick cell anaemia and other haemolytic disorders.⁹⁻¹⁰

In Sick cell anemia and other haemolytic disorders, intravascular haemolysis releases red blood cell Hemoglobin and arginase into the plasma. Plasma Hemoglobin scavenges and destroys nitric oxide while arginase interferes with further nitric oxide production by depleting arginine, an important substrate in nitric oxide production. A relative nitric oxide - deficient state ensues, leading to vasoconstriction and eventually remodelling of pulmonary vessels.¹¹⁻¹³

Sickle cell disease patients with pulmonary hypertension presented with disease related symptoms at an earlier age i.e. 4.15 ± 3.11 years as compared to those who had normal pulmonary hypertension (5.4 ± 2.91) which was statistically significant. Since the mean age of developing pulmonary hypertension in our study was less, we would like to suggest early screening for pulmonary hypertension. This would help to know the baseline status and decrease the morbidity. However larger studies are required to comment on the earliest age for screening for pulmonary hypertension. Klings ES et al says that in children elder than 8 years old the TRV determines morbidity risk, rather than mortality risk, and provides a baseline for future comparisons.¹⁴

In our study, the markers of haemolysis such as high reticulocyte count ($p = 0.036$), increased unconjugated serum bilirubin ($p = 0.041$), raised serum Lactate Dehydrogenase (LDH) ($p = 0.045$) had significant association with raised pulmonary hypertension. Cox et al hypothesized that Unconjugated bilirubin concentrations were higher in children with TRV over 3 m/s ($P=0.059$ for trend) but there was no evidence of any difference in LDH across the TRV categories.¹⁵⁻¹⁷

Following variables in treatments were found significant amongst patients with increase pulmonary hypertension. Number of packed red cell transfusions required in patients with pulmonary hypertension was 6.1 ± 8.31 times/year as compared to those with normal pulmonary hypertension (3.4 ± 7.04 times/year) which was statistically significant. The age at which first packed red cell transfusion given had no correlation with pulmonary hypertension ($p = 0.641$). This suggests that better management of crisis and overall health status plays an important role in manifesting complications rather than age at first transfusion.

The mean haemoglobin at diagnosis of disease was 6.3 ± 2.60 gm% amongst the patients with pulmonary hypertension which improved to 9.2 ± 1.24 gm% on treatment. However the rise in haemoglobin amongst those who did not have pulmonary hypertension was better. It

improved from 7.2 ± 1.76 gm% to 9.5 ± 1.76 gm%, though this was statistically not significant. ($p = 0.496$). However the rise in haemoglobin could not be evaluated accurately as patients also received packed red cell transfusion during the period of crisis. Grune and Stratton suggested in their book that validated haemolytic component may be useful to explore as a potential biomarker to assess efficacy in future clinical therapeutic trials.¹⁸ Zimmerman et al suggested in their study that Randomized paediatric trials with HU have demonstrated decreased painful episodes, acute chest syndrome, hospitalization transfusion and splenic auto infarction and improved quality of life. Prolonged use sustains the laboratory effects of decreased anaemia, markers of haemolysis, white blood cell and platelet counts and increased red cell mean corpuscular volume.¹⁹

In sickle cell patients with raised pulmonary hypertension, hydroxyurea had been started at an earlier age (mean 6 \pm 2.90 years) as compared to those with normal pulmonary hypertension. (6.9 ± 3.84 years) which was statistically significant. The mean dose of Hydroxyurea was higher (20.5 ± 5.55) mg/kg/day amongst those with raised pulmonary hypertension than those with normal pulmonary pressure (19.7 ± 4.93 mg/kg/day). This was statistically significant. ($p = 0.045$). Bruce w. Thompson et al in their phase 3 clinical trial to test whether treating young children ages 9 to 17 months at entry with a liquid preparation of hydroxyurea (20 mg/kg/day for two years) can decrease organ damage in the kidneys and spleen by at least 50%. A definitive clinical trial showing that hydroxyurea can also prevent organ damage might support widespread use of the drug at an early age.²⁰

MCV baseline before starting Hydroxyurea was 76.1 ± 10.39 $\mu\text{m}^3/\text{dl}$ which improved to 85.2 ± 9.70 $\mu\text{m}^3/\text{dl}$ which was statistically significant ($p = 0.043$). Green NS and Barral S et al study concluded that Hydroxyurea is a remarkably effective drug for a large proportion of children with SCD. Hydroxyurea is the sole approved pharmacologic therapy for sickle cell disease (SCD).^{7,21} Castro OL, Gordeuk VR et al and Minniti CP, Wilson J et al in their studies suggested that drug may have been effective in patients with more severe haemolytic anaemia, as characterized by a high quartile haemolytic component and, if taken with hydroxyurea to limit vaso - occlusive complications, could conceivably improve haemoglobin oxygen saturations and reduce the risk of pulmonary and systemic hypertension, leg ulcers, and death.²²

In our study the marker of pulmonary hypertension was TR Jet velocity. According to AAP classification, pulmonary hypertension divides in normal, mild and moderate pulmonary hypertension.¹⁴ Accordingly out of 19 (38%) patients with pulmonary hypertension, 12 (63.15%) patients had mild pulmonary hypertension and 7 (36.85%) patients had moderate pulmonary hypertension.

In our study there was no obvious chest x - ray finding suggesting of any correlation with early changes of pulmonary hypertension. Radiographic findings may initially be normal in patients with acute chest syndrome. However, Leong C et al said in their publication that findings in the radiography of the thorax include an increase in the size of central pulmonary arteries, with amputation

and loss of distal attenuation, as well as a cardiomegaly which is predominant in the right ventricle.²³

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