

AN OBSERVATIONAL STUDY TO DETERMINE THE PREVALENCE OF PULMONARY HYPERTENSION IN CHILDREN WITH SICKLE CELL DISEASE

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Abstract

Background: Pulmonary hypertension may develop in most forms of hereditary and chronic hemolytic anemia during intravascular hemolysis. Cross-sectional studies have found associations between the degree of hemolysis and marker of pulmonary artery pressure in individual with sickle cell anemia. Elevated tricuspid regurgitation velocity and left ventricular diastolic dysfunction develop in children with sickle cell anemia, but the clinical importance is unclear. Pulmonary hypertension (PHT) is a widely recognized complication of hereditary hemolytic anemia including sickle cell anemia, thalassemia, hereditary spherocytosis and paroxysmal nocturnal haemoglobinuria. **Materials and Methods:** This is an Observational study was conducted at Paediatrics Haematology-Oncology Division at a tertiary care hospital in a metropolitan city over a period of 1 year. 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. HbS/β+ Thalassemia who were registered at our Centre for regular treatment. All children with Sickle cell syndromes (diagnosed on HPLC) who were following up in the Paediatric Haematology Clinic at a tertiary care hospital were screened for the study. The first 50 children who fulfilled the inclusion criteria were enrolled into the study. **Result:** Out of 30 male patients, 8 had mild pulmonary hypertension, 5 had moderate pulmonary hypertension and 17 patients had normal pulmonary hypertension. Out of 20 female patients, 4 had mild pulmonary hypertension, 2 had moderate pulmonary hypertension and 14 patients had normal pulmonary hypertension. Total 46 patients showed crisis of different types of which vaso occlusive crisis was most common seen in 36 (72%) patients. In our study severity of pulmonary hypertension in various types of crisis. Out of 50 patients 12 (24%) patients had mild pulmonary hypertension, 7 (14%) had moderate pulmonary hypertension and 31 (62%) had normal pulmonary hypertension. The maximum no. of patients i.e. 36 patients were amongst those with bony crisis. 8/36 (22%) had mild pulmonary hypertension, 4/36 (11.1%) had moderate pulmonary hypertension. Though only 2 patients had acute chest syndrome, both showed moderate pulmonary hypertension. **Conclusion:** High pulmonary artery pressures do occur in children with sickle cell disease. Screening by echocardiography can lead to early detection and intervention that may potentially reverse this disease process. Radiological changes were not a good indicator for diagnosing pulmonary hypertension. Electrocardiogram studies correlated better with pulmonary hypertension.

INTRODUCTION

Sickle cell anemia was first described in a West Indian dentistry student, Walter Clement Noel, by Herrick and Irons in 1910.^[1] Sickle cell anemia, though rare in India, with a gene frequency of 4.3%, occurs in wide geographical distribution from Orissa, Maharashtra, Madhya Pradesh and Jharkhand. Sickle cell disease is a congenital structural haemoglobinopathy, inherited in an autosomal recessive manner.^[2] It is caused by a single point mutation in the β -globin gene that changes the sixth amino acid from glutamic acid to valine.^[3]

Sickle cell anemia includes both homozygous SS and heterozygous AS state. In homozygous state, mutation occurs in both alleles in beta-globin chain {HBS>50%} and in heterozygous state, mutation occur in one alleles in beta-globin.^[4] HBS makes cell rigid, especially when cells are exposed low oxygen levels.^[5] The red blood cells becomes shaped like crescents or sickles and lead to vaso-occlusive crisis and other acute manifestations like acute chest syndrome, stroke, increased susceptibility to infection and aplastic crisis.^[6]

Pulmonary hypertension may develop in most forms of hereditary and chronic hemolytic anemia during intravascular hemolysis. Cross-sectional studies have found associations between the degree of hemolysis and marker of pulmonary artery pressure in individual with sickle cell anemia.^[7] Elevated tricuspid regurgitation velocity and left ventricular diastolic dysfunction develop in children with sickle cell anemia, but the clinical importance is unclear.^[8] 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 and association with mortality during the short duration of follow up has not been observed.^[9]

Pulmonary hypertension (PHT) is a widely recognized complication of hereditary hemolytic anemia including sickle cell anemia, thalassemia, hereditary spherocytosis and paroxysmal nocturnal haemoglobinuria.^[10] It occurs in 32% of adults with sickle cell anemia and is associated with an increased risk of mortality.^[11] 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%.^[12]

MATERIALS AND METHODS

This is a Observational study was conducted at Paediatrics Haematology-Oncology Division at a tertiary care hospital in a metropolitan city over a period of 1 year.

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. HbS/ β + Thalassemia who were registered at our Centre for regular treatment.

Exclusion Criteria

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

Methods

All children with Sickle cell syndromes (diagnosed on HPLC) who were following up in the Paediatric Haematology Clinic at a tertiary care hospital were screened for the study. The first 50 children who fulfilled the inclusion criteria were enrolled into the study. 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, hepatosplenomegaly and stigmata of crisis. All children were administered standard care including penicillin prophylaxis, vaccination for encapsulated organisms, Zinc and hydroxyurea if indicated.^[13] Detailed treatment history of hydroxyurea,^[14] including age of starting HU, dose at initiation and at maintenance as well as any toxicity related to drug causing discontinuation were noted. All children were subjected to the following investigations:

- Complete hemogram with reticulocyte count
- Liver function tests, Renal function tests with lactate dehydrogenase (LDH) for monitoring of hemolysis and drug toxicity
- A chest radiograph, an electrocardiogram and a 2D Echocardiogram to evaluate for pulmonary hypertension and any other abnormalities
- 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 was performed according to the guidelines of American Society of Echocardiography. (15) TRV was measured by pulsed-wave and continues wave Doppler echocardiography where 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).

Statistical Analysis

The methods and results are illustrated in the form of tables and graphs. All relevant data is compiled and entered into computer using computer-based

software SPSS for appropriate analysis. Quantitative variable has been presented by mean + standard deviation, Frequency and percentage are computed according to the data. Quantitative data was analyzed by proportion and Chi square test at $p < 0.05$ level of significance.

RESULTS

[Table 1] shows Age and Gender distribution. Maximum number of children 25 (50%) were in the age group of 11 to 15 years with 15 males and 10 females, followed by 20(40%) in the age group of 5 to 10 years and 5 (10%) in the age group of 15 to 18 years.

In this [Table 2] out of 50 patients, 12 (24%) patients had mild pulmonary hypertension, 7(14%) patients had moderate pulmonary hypertension and 31(62%) patients had normal pulmonary hypertension. there was no severe pulmonary hypertension in this study. As revealed in [Table 3], most common presenting symptom was painful crisis, which was seen in 35 (70%) patients followed by fever with pallor which was seen in 13(26%) patients.

This tables shows the association of age of the patients with pulmonary hypertension. 21 patients belonged to age between 5-10 years, of which 4 patients had mild pulmonary hypertension, 3 patients had moderate pulmonary hypertension and 14 patients had normal pulmonary hypertension. 24 patients belonged to age between 11-15 year, of which 8 patients had mild pulmonary hypertension, 4 patients had moderate pulmonary hypertension and 12 patients had normal pulmonary hypertension. 5 patients who belonged to age more than 15 had normal pulmonary hypertension. p value of this table was 0.297 which suggests that association of age of patients with pulmonary hypertension was not significant. [Table 4]

As shown in [Table 5], Out of 30 male patients, 8 had mild pulmonary hypertension, 5 had moderate pulmonary hypertension and 17 patients had normal pulmonary hypertension. Out of 20 female patients, 4 had mild pulmonary hypertension, 2 had moderate pulmonary hypertension and 14 patients had normal pulmonary hypertension. Male to female ratio was 3:2. p value of this table was 0.623 which suggest that

association of gender of patients with pulmonary hypertension was not-significant.

[Table 6] demonstrates the occurrence of pulmonary hypertension based on the types of sickle syndrome. Out of 50 patients 26 (52%) were sickle cell homozygous, 22 (44%) patients were HbS/ β^+ thalassemia and 2 (4%) patients were HbS/ D disease. Amongst sickle cell homozygous patients, 10/26 (38%) patients had pulmonary hypertension. And amongst HbS/ β^+ thalassemia patients, 8/22 (36%) had pulmonary hypertension, Of the 2 patients with HbS/ D disease, only 1 patient had mild pulmonary hypertension. ($p=0.365$) the difference in pulmonary hypertension amongst sickle homozygous and heterozygous state was statistically not significant.

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. The markers of hemolysis as pallor ($p = 0.046$), high reticulocyte count ($p = 0.036$), increased unconjugated serum bilirubin ($p = 0.041$), rise in LDH ($p = 0.045$), Number of crises till study time ($p=0.048$), Number of packed cell transfusion requirement ($p=0.043$) had significant association with raised pulmonary hypertension. 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 ($p = 0.043$). However the rise in hemoglobin on hydroxyurea was better in patients with normal Pulmonary pressure. ($p=0.049$).

[Table 7]

Total 46 patients showed crisis of different types of which vaso occlusive crisis was most common seen in 36 (72%) patients. [Table 8]

[Table 9] describe severity of pulmonary hypertension in various types of crisis. Out of 50 patients 12 (24%) patients had mild pulmonary hypertension, 7 (14%) had moderate pulmonary hypertension and 31 (62%) had normal pulmonary hypertension. The maximum no. of patients i.e. 36 patients were amongst those with bony crisis. 8/36 (22%) had mild pulmonary hypertension, 4/36 (11.1%) had moderate pulmonary hypertension. Though only 2 patients had acute chest syndrome, both showed moderate pulmonary hypertension.

Table 1: Age and Gender Distribution of Patients (n=50)

Present Age (years)	Male	Female	Total (%)
5 to 10	11	9	20 (40%)
11 to 15	15	10	25 (50%)
15 to 18	4	1	5 (10%)
Total	30	20	50 (100%)

Table 2: Correlation with Severity of Pulmonary Hypertension (PHT) in Sickle Cell Disease (n=50)

PHT	Number of patients	Percentage
No PHT	31	62.0%
Mild	12	24.0%
Moderate	7	14.0%
Severe	0	0.00%

Table-3: First Presenting Symptoms (n=50)

First Presenting Symptoms	NO.	Percent
Painful Crisis	35	70.0
Fever with Pallor	13	26.0
Lump in Abdomen	1	2.0
Pallor	1	2.0
Total	50	100.0

Table 4: Correlation of Prevalence of PHT in Various Age Groups

Age Vs PHT		PHT			Total
		Mild	Moderate	Normal	
Age (Years)	5 to 10	4 19.0%	3 14.3%	14 66.7%	21 100.0%
	11 to 15	8 33.3%	4 16.7%	12 50.0%	24 100.0%
	> 15	0 0.0%	0 0.0%	5 100.0%	5 100.0%
Total		12 24.0%	7 14.0%	31 62.0%	50 100.0%

Table 5: Correlation of Prevalence of PHT with Gender

Correlation of Pulmonary Hypertension in different Gender				
Gender	PHT			Total
	Mild	Moderate	Normal	
Female	4 20.0%	2 10.0%	14 70.0%	20 100.0%
	8 26.7%	5 16.7%	17 56.7%	30 100.0%
Male	12 24.0%	7 14.0%	31 62.0%	50 100.0%
	12 24.0%	7 14.0%	31 62.0%	50 100.0%

Table 6: Correlation of Prevalence of Pulmonary hypertension with Types of Sickle Cell Disease

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

Table 7: Association of various Factors with PHT

Group Statistics								
	PHT	N	Mean	SD	SE of Mean	T value	P value	Significance
Age at first symptom	No	31	5.4839	2.91971	.52440	2.374	0.041	Yes
	Yes	19	4.1579	3.11383	.71436			
No. of crisis in lifetime	No	31	1.2903	1.24348	.22334	1.965	0.048	Yes
	Yes	19	2.4737	2.96963	.68128			
No of VO crisis	No	31	1.3548	.984	.17495	2.130	0.046	Yes
	Yes	19	1.7368	1.77375	.40693			
Hemoglobin Baseline	No	31	7.2581	1.76951	.31781	1.993	0.046	Yes
	Yes	19	6.3158	2.60454	.59752			
Hemoglobin on treatment	No	31	9.5806	1.76587	.31716	0.686	0.496	No
	Yes	19	9.2632	1.24017	.28451			
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	.21169	2.156	0.036	Yes
	Yes	19	4.4211	2.00875	.46084			
Total bilirubin	No	31	1.5806	1.31083	.23543	2.383	0.041	Yes
	Yes	19	2.4211	1.60955	.36926			
Indirect bilirubin	No	31	0.8710	1.14723	.20605	2.303	0.045	Yes
	Yes	19	1.7368	1.28418	.29461			
Serum LDH	No	31	996.7742	374.87035	67.32870	2.127	0.045	Yes
	Yes	19	885.7895	265.21429	60.84433			

Age of 1st transfusions	No	31	4.8065	3.48730	.62634	0.47	0.641	No
	Yes	19	5.2632	3.07033	.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	.69015	1.943	0.049	Yes
	Yes	19	6.0000	2.90593	.66667			
HU mean dose	No	31	19.7419	4.93266	.88593	2.108	0.045	Yes
	Yes	19	20.5789	5.55093	1.27347			

Table 8: Type and No. of Crisis in Sickle Cell Disease

Type of Crisis	No	Percent
Bony crises	36	72.0
No Crisis	4	8.0
Vo+ Hemolytic	4	8.0
Acute Chest Syndrome	2	4.0
Sickle Hepatopathy	2	4.0
Hemolytic	1	2.0
Splenic Sequestration	1	2.0
Total	50	100.0

Table 9: Correlation of Crisis with PHT

Types of crisis	PHT			Total
	Mild	Moderate	Normal	
Bony crises	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%)

DISCUSSION

We studied the prevalence of pulmonary hypertension in 50 patients of sickle cell disease. The demographic characteristics of the study population are as depicted in [Table 1-3]. As shown, patients in our study ranged in the age group of 5 to 18 years. 21 (42%) patients belonged to the age group of 5 to 10 years, 24 (48%) were between 11 to 15 years and 5(10%) were more than 15 years. There were 30 (60%) males and 20 (40%) females with male to female ratio of 3:2. V.R. Gordeuk et al. in their study have included patients in the age group of 3 to 20 years was had sickle cell disease. (16) The mean age of our study population was 11.30 ± 3.74 years, while in a study done by R.I. Liem et al., the mean age at study enrolment was 14.02 ± 2.62 years and male to female sex ratio was 3:2.1 which was similar to our study.^[17]

Out of 30 male patients, 8 (26.6%) had mild pulmonary hypertension, 5 (16.7%) had moderate pulmonary hypertension and 17 (56.7%) patients had no pulmonary hypertension. Out of 20 female patients, 4 (20%) had mild pulmonary hypertension, 2 (10%) had moderate pulmonary hypertension and 14 (70%) patients had no pulmonary hypertension. Male to female ratio was 3:2. ($p = 0.623$) which suggest that association of gender with pulmonary hypertension was non-significant. Lamacarre et al., in their study showed male gender, increased triglycerides level, BMI and blood viscosity could

increase the risk for developing relative hypertension in sickle cell disease.^[18]

Out of 50 patients, 26 (52%) patients were sickle cell homozygous, 22 (44%) were HbS/ β^+ thalassemia and 2 (4%) patients were sickle HbS/D disease. As in our study overall prevalence of pulmonary hypertension was 38%. Amongst sickle cell homozygous patients, 10/26 (38%) patients had pulmonary hypertension. And amongst HbS/ β^+ thalassemia patients, 8/22 (36%) had pulmonary hypertension. Of the 2 patients with HbS/ D disease, only 1 patient had mild pulmonary hypertension. In our study, sickle cell homozygous had more common pulmonary hypertension as compared to heterozygous HbS/ β^+ thalassemia disease, though it was statically not significant ($p = 0.365$). Farzana D. et al., in their study, had mild to moderate pulmonary hypertension as more common in sickle cell homozygous as compared to HbS/ β^+ thalassemia disease ($p = 0.27$).^[19]

In our study showed the types and frequency of crises till the study period. The most common crises were Vaso-occlusive crisis, which was seen in 34 (68%) patients followed by 4 (8%) had combination of vaso occlusive and hemolytic crisis. 2 (4%) each had acute chest syndrome and hepatopathy. 4 (8%) patients did not have any episode of crisis in their life till the recent follow-up and only 1(2%) patient had splenic sequestration. The association of pulmonary hypertension with crisis showed that out of 19 patients with pulmonary hypertension, 12 had vaso-occlusive crisis, 2 had acute chest syndrome and 1 had hemolytic crisis. Only 2 patients who had

pulmonary hypertension had no crisis in their life till the recent follow-up, Steven J, Ambrusko et al in their study of 224 SCD patients, (11 of 44) (26.2%) with TRV \geq 2.5 m/sec were compared to 31 patients without elevated TRV. No significant differences were observed for frequency of vaso occlusive crisis and acute chest syndrome amongst patients of pulmonary hypertension.^[20]

In our study the marker of pulmonary hypertension was TR Jet velocity. According to AAP classification,^[21] pulmonary hypertension divides in normal, mild and moderate pulmonary hypertension. 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 the comparisons of pulmonary hypertension with 2D ECHO done before 1 year back in 11 patients. 4 patient had pulmonary hypertension of which 2 had mild and 2 had moderate pulmonary hypertension. On follow-up 2D ECHO there was no correlation with hemolysis factors and crisis that changes TR Jet velocity as the TR Jet velocity has changed from 28.87 to 29.75 which was not statistically significant ($p = 0.658$). Eduardo Bossone et al., said that the nonspecific nature of its early symptoms and signs, pulmonary arterial hypertension (PAH) is often diagnosed in its advanced stages.^[22]

In our study there were no or mild changes seen in Electrocardiogram that suggested of early Right ventricle changes but not obvious pulmonary hypertension findings seen in our patients. Anjan S. Batra et al depicts in their study that in Paediatrics population, ECG analysis did not add any new information to that already known by echocardiography. The amplitude of the S waves in lead I and of the V1 and R waves in lead V6 are conventionally used to evaluate left ventricular hypertrophy. However, we found only a weak correlation of the amplitude of the R wave in lead V6 with the degree of anemia. There was no evidence of ischemia by ST segment or T wave changes.^[23]

CONCLUSION

High pulmonary artery pressures do occur in children with sickle cell disease. Screening by echocardiography can lead to early detection and intervention that may potentially reverse this disease process. Radiological changes were not a good indicator for diagnosing pulmonary hypertension. Electrocardiogram studies correlated better with pulmonary hypertension.

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