Original Research Article

Pediatric Education and Research
Volume 7 Number 1, January-March 2019
DOI: https://dx.doi.org/10.21088/per.2321.1644.7119.2

The Study of Prevalence of Pulmonary Hypertension in Children with Sickle Cell Disease

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Abstract

Objective: To assess the prevalence and the risk factors of pulmonary hypertension in children with sickle cell disease.

Methods: Children (age: 3- 15 y) diagnosed with sickle cell disease were included in the study conducted between August 2016 to July 2018. All relevant past history of hospitalisation, crisis (esp. acute chest syndrome crisis), blood transfusion and medication history was recorded. A thorough physical examination, blood investigations (CBC and Reticulocyte Count) and 2D Echocardiography was carried out for all the enrolled patients.

Results: In this study, 18.57% of the study population was found to have PAH with TRV > 2.5 m/s. No statistically significant co-relation was found between age, gender, religion, anthropometry, blood group type, sickle phenotype, total leukocyte count and PAH. There was a statistically significant association of pulmonary hypertension with low Hb, high reticulocyte count and platelet count, history of repeated hospital admissions and blood transfusions and a positive history of ACS.It was also found that patients who were on hydroxyurea treatment were less likely to develop PAH.

Conclusion: One-fourth of pediatric sickle cell disease patients demonstrated presence of pulmonary hypertension. Risk factors like low Hb, elevated platelet and reticulocyte count, repeated number of hospital admissions, episodes of ACS and blood transfusions were significantly associated with an elevated TRV finding on Echocardiography in children with Sickle Cell Disease. Hydroxyurea therapy too played a significant role in this study in reducing the chances of having PAH. These patients need to be monitored and followed-up after treatment to assess need for later treatment

Keywords: Sickle Cell Disease; Pulmonary Hypertension; Doppler Echocardiography; Tricuspid Regurtiant Velocity

Introduction

Sickle cell disease is a group of inherited red blood cell disorders. The first account of what was then called sickle cell anemia in the medical literature was in 1910 by James B. Herrick, a Chicago physician who described the symptoms in a black male student from the West Indies [1]. Hemoglobin is a protein in red blood cells that carries oxygen throughout the body. With SCD, the hemoglobin forms stiff rods within the red blood cells. This results in changes in the shape of the red blood cells. The normal discoid shaped cells are changed into a crescent, or sickle, shape during periods of stress. The sickle-shaped cells are not flexible and do not change shape easily.

Primary pulmonary hypertension is a progressive disease that is characterized by restricted blood flow in the pulmonary vasculature, resulting in an increase in pulmonary vascular resistance (PVR) [2]. Patients with sickle cell disease (SCD), a monogenic blood disorder that causes red blood cells to form a sickle shape and decreases their ability to carry oxygen to the body's tissues, can develop secondary pulmonary hypertension. Although there is significant data showing that pulmonary hypertension secondary to SCD increases morbidity and mortality in adult

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Received on 15.12.2018, **Accepted on** 14.01.2019

patients, there is little information regarding how PAH affects children with SCD [3]. Diagnosing PAH requires right heart catheterization, however, the American College of Cardiology Foundation and the American Heart Association recommend using Doppler Echocardiography as a screening test for PAH as Doppler echocardiography is non-invasive, there is much more information available regarding TRV than right heart catheterization, an invasive procedure that cannot be used as a routine screening tool. This study examines the prevalence and incidence of elevated TRV (≥ 2.5 m/s) in children with SCD as well as factors that may be associated with an elevated TRV [2].

Methods

The patients enrolled were children of 3-15 years of age with sickle cell disease who came for regular follow up in the Sickle Cell Clinic conducted weekly at Acharya Vinoba Bhave Rural Hospital, Maharashtra, India during August 2016 to July 2018. In the course of their visit/ hospital stay, detailed history was taken, physical examination was performed and laboratory tests were done which included a complete blood count and reticulocyte count. Echocardiograms were performed when patients were in a steady state.

For this study all patients who underwent a screening echocardiogram were included. Patients with known congenital or acquired cardiac diseases or those who had any other conditions other than SCD/SCA affecting myocardial performance were excluded from the study. Medical charts were reviewed for clinical and laboratory data and results of imaging studies. The study was approved by the Ethics Committee, JNMC, Wardha.

Echocardiography

Pulmonary artery hypertension (PAH) was taken as pulmonary artery systolic pressure of >30 mm Hg corresponding to a peak tricuspid regurgitant jet velocity of >2.5 m/s [4].

The left ventricular end systolic and end diastolic dimension, left ventricular posterior wall thickness and septal thickness were measured by m-mode reading. The left ventricular ejection fraction percentage was calculated using the formula:

EF= (Dd) 3-(Ds) 3/ (Dd) 3 x 100

The normal mean ejection fraction is 74% with 95% predicting limits of 64-83. The mean normal value is 36% with 95% prediction limit of 28-44%. The above values were recorded at a frame speed of 1mm/sec. To record left ventricular inflow velocities, the apical four-chamber view was used, and the pulsed-wave Doppler sample volume was placed at the level of the leaflets tips of the mitral valve, where the highest peak velocity was recorded. Peak flow velocities of the left ventricular inflow in early diastole (E) and late diastole with atrial contraction (A) were measured from the baseline to the maximum flow velocity. An E/A velocity ratio was calculated for each cardiac cycle [5].

Data Analysis

Clinical characteristics were compared between patients with and without PAH. Statistical analysis was done by using descriptive and inferential statistics using chi-square test and student's unpaired t test and Multiple Regression Analysis and software used in the analysis were SPSS 22.0 version and GraphPad Prism 6.0 version. The Z score was calculated. A p value less that 0.05 was considered significant.

Results

A total of 77 patients with sickle cell disease were followed up in the Sickle Cell Clinic, AVBRH, Wardha. Out of the 77 patients, 70 were eligible for the study. Medical history, physical examination and echocardiogram were obtained for all 70 patients.

1) Prevalence of pulmonary arterial hypertension:

18.57% (13 out of 70) of the patients with sickle cell disease had a peak TRV > 2.5 m/s, corresponding to pulmonary arterial pressures of >30 mmHg. The prevalence of pulmonary pressures did not vary with age (p=0.098)

2) Risk factors of elevated pulmonary artery pressures:

The table 1 below compares the demographic and clinical data of patients with and without elevated pulmonary artery pressures. All the 13 patients that had elevated TRVs (>2.5 m/s) were diagnosed to have Hb- SS on Hemoglobin Electrophoresis. There was no difference for age or gender between the affected and unaffected group. Patients with elevated pulmonary artery pressures had significantly higher rated of hospital admissions, episodes of ACS and history of receiving blood transfusions. Laboratory investigations revealed

that patients with elevated pulmonary pressures also had a lower mean haemoglobin, higher platelet count and reticulocyte count as compared to patients without PAH.

It was also noted that patients receiving hydroxyurea treatment were at lower risk of developing PAH as compared to those who did not receive hydroxyurea.

Table 1: Clinical Characteristics of study participants

S. No.	Patient Characteristics	TRV		P value
		>2.5 m/s	< 2.5 m/s	
	Demographics and Phenotype			
1.	Age (years)	9.84±3.21	7.36±3.65	0.098
2.	Female sex, n (%)	7(53.85%)	20(35.09%)	0.21
3.	Hemoglobin SS, n (%)	13(100%)	47(82.46%)	0.26
	History and Physical Examination			
1.	Number of hospital admissions (mean + SD)	5.69±2.28	3.05±2.14	0.001
2.	Crisis episodes (>5 times) (n, %)	6(46.15%)	1(1.75%)	0.0001
3.	Number of blood transfusions (mean + SD)	4.76±1.69	2.85±2.21	0.025
4.	Heart Rate (/min)	100.30±9.72	102.42±11.95	0.50
5.	Respiratory Rate (/min)	20.92±3.22	22.10±3.19	0.23
6.	Systolic blood pressure (mmHg)	106.46±11.55	101.29±6.73	0.05
7.	Diastolic blood pressure (mmHg)	68.92±8.23	67.08±5.05	0.30
8.	Oxygen saturation (%)	98.38±1.12	98.42±1.13	0.91
	Laboratory tests			
1.	Haemoglobin (g/dL)	4.13±0.91	8.72±1.84	0.0001
2.	Total Leucocyte Count (x103/L)	9076.92±1888.18	9780.70±2905.01	0.40
3.	Platelet Count (103/mm3)	2.92±1.60	2.24±0.78	0.030
4.	Retic Count (%)	1.27±0.17	0.89±0.24	0.0001
	Hydroxyurea treatment (n,%)	2(2.86%)	31(44.29%)	0.044

Table 2: Logistic regression analysis of predictors of PAH

	Unstandardized Coefficients		Standardized Coefficients	t	p-value
	B	Std. Error	Beta		
PAH	2.335	0.377			
Hospital admissions	0.031	0.012	0.260	2.601	0.012,S
VOC	-0.010	0.033	-0.028	0.305	0.762,NS
ACS	-0.079	0.019	-0.367	4.184	0.0001,S
Height	-0.004	0.002	-0.149	1.950	0.056,NS
Elevated Retic Count	-0.378	0.101	-0.270	3.761	0.0001,S
Low O2 saturation	-6.064E-5	0.000	-0.016	0.243	0.809,NS
High Plt count	-0.075	0.026	-0.193	2.861	0.006,S
Low Hb	0.074	0.016	0.468	4.533	0.0001,S

Discussion

PHTN is a well-described, serious, and potentially lifethreatening complication of hemolytic anemia disorders, including SCD [4,6-13]. While the occurrence of PHTN in adults with SCD is well documented [4,14-21], little is known about its incidence and characteristic presentation in children with SCD. This study provides an initial characterization of pediatric sickle cell patients with presumed PHTN, as detected by TRV of 2.5 m/sec on echocardiography . The overall prevalence of elevated pulmonary artery pressure was 18.57%, which is similar to the prevalence reported in previous retrospective pediatric studies [22,23].

In a study done by Minniti et al. [23], 11% prevalence of PAH was reported out of the total pateints enrolled into the study. Qureshi et al. [22] did a case-control comparison of echocardiograms of patients with sickle cell disease and healthy control subjects and reported a 16% prevalence of

PHT; however these studies were retrospective and only a subset of the eligible patients was included.

On evaluation of risk factors for elevated pulmonary artery pressures, we found no correlation between age and PAH. In the present study maximum cases of SCD that presented with PAH to our hospital come under age group of 8-12 years, which is 53.85% of the total patients with PAH. The youngest patient with PAH in our study was 5 years old. A similar observation was made by Qureshi et al. [22] in their study of sickle cell patients from ages 6 months to 21 years in which the youngest child with elevated TRV was 9 years old and no correlation was found between age and PAH. Ambrusko et al. [24] studied the prevalence of pulmonary arterial hypertension among the sickle cell disease children with mean age group of 12.9 years. They too found no correlation between age and pulmonary hypertension.

Similarly no correlation was found between developments of PAH and gender, religion or ABO set up.

The correlation observed in this study between elevated TRV and degree of anemia, thrombocytosis and reticulocytosis suggests role for hemolysis in the development of HTN. This is Consistent with the observations by Gladwin et al. [4,25]. Hyperhemolysis leads to free plasma hemoglobin that both scavenges nitric oxide and induces oxygen free radical formation and may cause acute and chronic pulmonary vasoconstriction and vaso-proliferation that may contribute to the development of PHTN,stroke, priapism and leg ulcers [1,26,27].

In the present study, patients who had more episodes of hospital admissions and episodes of ACS were more likely to be at risk of developing PAH (p= 0.0001). This correlation can be explained by the hypoxic response in the pathogenesis of acute chest syndrome due to pulmonary vaso-occlusion, ischemia and endothelial dysfunction leading to pulmonary arterial hypertension [28].

The majority of patients with elevated TRV gave history of repeated transfusion therapy at the time increased TRV was detected, suggesting that transfusion-associated complications, such as iron overload, may play a causative role for PAH.

A major drawback of our study was conducted in a rural tertiary care hospital, so the findings of the study cannot be generalized to the population as a whole. This is the inherent limitation of a hospital based study compared to community based study. By this the exact prevalence of PAH could not be determined. Also, the sample size of this study is small, therefore leading to difficulty in applying the findings of the study to the general population.

PAH is a serious complication in adults with sickle cell disease and a common cause of mortality amongst them. Our study shows that this complication begins early in childhood. Therefore, early detection of elevated pulmonary artery pressures in childhood and appropriate intervention with optimization of anti-haemolytic therapy may prevent progression of this complication and thereby reduce morbidity and mortality associated with PAH. In addition, newer pharmacologic therapies for the treatment of PAH, such as sildanefil and other vasodilators, may have therapeutic benefit to these patients. We therefore recommend that screening transthoracic echocardiography be incorporated into the routine annual evaluation for children with sickle cell disease.

Conclusion

Our study identified an important aspect of sickle cell disease which may have long-term implications in a significantly high number of patients who are already at risk of developing pulmonary hypertension. Based on our present results, we suggest routine screening in patients with sickle cell disease by Doppler echocardiography, for early detection of development of PAH. Patients with low haemoglobin, high platelet and reticulocyte count with history of repeated hospital admissions, blood transfusions or episodes of ACS crisis may form a sub set of patients that need to be evaluated more thoroughly.

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