Original Research Article

Pulmonary arterial hypertension in children with sickle cell anaemia

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Abstract

Background: Pulmonary hypertension(PHT) is a life threatening complication which occurs in adults with sickle cell disease(SCD). But there is paucity of knowledge about prevalence of pulmonary hypertension in Paediatric SCD population.**Objective:**To find out the prevalence of pulmonary hypertension in children with SCD.**Methods:**552 children age between 5 to 14 years were enrolled after written informed consent was obtained from parents/guardian. Children with Congenital heart disease, pulmonary stenosis, Rheumatic heart disease were excluded from the study. PHT in all cases of with SCD children was screened by using 2D Echocardiography in the department of cardiology. PHT is defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest. All the data were validated and analyzed with SPSS version 25.**Results:**Overall prevalence of pulmonary hypertension in our study is 20.4%. Of these, 6.5% subjects have mild and 13.9% subjects have moderate pulmonary hypertension. Low haemoglobin (p=0.021), high number of crisis (p=0.000), high number of blood transfusion (p=0.000), presence of loud second heart sound (p=0.000) and presence of Parasternal heave (p=0.000) were significantly associated with pulmonary hypertension. The prevalence of pulmonary hypertension in children with SCD demonstrated an increase in trend with age.**Conclusion:**High pulmonary artery pressures do occur in children with SCD. Screening by echocardiography can lead to early detection and intervention.

Keywords: Sickle cell disease (SCD), Pulmonary Hypertension (PHT), Pulmonary Artery Systolic Pressure (PASP).

Introduction

Sickle cell disease is a congenital structural haemoglobin-opathy, inherited in an autosomal recessive manner. It is one of the commonest disorders occurring with a prevalence rate of 20-25 million worldwide [1]. Sickle cell anaemia with prevalence of heteozygotes varying from 1-40 per cent occurs in geographical distribution from Odisha, Maharashtra, Madhya Pradesh and Jharkhand [2].

Morbidity from SCD may be due to anaemia, acute chest syndrome, infection, stroke, pulmonary hypertension, nephropathy [3].Common causes of death are infection, stroke, splenic sequestration, renal failure, pulmonary hypertension, left ventricular failure[4]. Pathogenesis of pulmonary hypertension appears to be multifactorial, including:haemolysis induced endothelial dysfunction, chronic hypoxemia, chronic thromboembolism, intravascular sequestration of sickle red cells and iron overload [5]. Intravascular haemolysis leading to nitric oxide deficiency as a major pathogenic mechanism for pulmonary hypertension in sickle cell anaemia and other haemolytic disorders [6,7]. It is associated with a significant several folds increased mortality rates to uncomplicated sickle cell anaemia [8].Pulmonary artery hypertension (PAH) is defined as a mean pulmonary artery pressure (mPAP) of greater than or equal to 25mmHg at rest as determined by cardiac catheterization irrespective of age except in infancy [9,10]. Early symptoms of pulmonary hypertension are similar to those of many other diseases that present with dyspnoea on exertion, thus delaying the diagnosis until the disease is far advanced [9,11].The gold standard of measurement of mean pulmonary artery pressure (mPAP) is by right sided heart catheterization, but this method is invasive and not suitable for screening purposes [5].

Two dimensional echocardiography is used to screen pulmonary hypertension by measuring pulmonary artery pressure.Pulmonary hypertension is a life threatening complication which occurs in 20% to 40% of adults with sickle cell disease [12]. It is a severe complication of sickle cell disease linked to accelerated mortality [12]. But there is paucity of knowledge about prevalence of pulmonary hypertension in paediatric SCD population in developing countries. Recent studies have shown that the prevalence of pulmonary hypertension in children is between 16% and 26.2% [12]. So we took this study to determine the prevalence of pulmonary hypertension in children with SCA in our population.

Objectives of the study: To estimate the prevalence of pulmonary arterial hypertension among children of sickle cell anaemia age group between 5-14 years in VIMSAR, Burla.

Materials and methods

The study was conducted in the department of Paediatrics and Sickle Cell Institute, Veer Surendra Sai Institute of Medical Sciences and Research, Burla from November 2018 to October 2020.

Study design: Observational-Cross-sectional study.

Study population: All clinically suspected subjects of sickle cell anaemia age group between 5 to 14 years attending OPD, IPD&

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sickle cell institute of VIMSAR during study period were included as the study population.

Inclusion criteria

1. Hb electrophoresis / HPLC confirmed subjects of sickle cell homozygous children of either gender aged between 5 to 14 years.

Exclusion criteria

1. Congenital heart disease
2. Pulmonary stenosis
3. Rheumatic heart disease
4. Patients with splenectomy.
5. Critically ill patients.

Data Analysis and Interpretation :Data collected from the study was processed, checked for internal errors, internal and external validation was done using n Master Version 2.0 software and SPSS v 25 software (IBM, New York). Data was analyzed and the result was interpreted. Continuous data were expressed in mean ± SD; categorical data were expressed in proportions. Data normalcy testing of continuous data was done by Shapiro Wilk's test. For all statistical purposes p value < 0.05 was considered significant.

Results

A total of 552 participants were enrolled in the data analysis for our study. Table 1 shows a summary of the demography and anthropometric findings in SCA subjects.

Table 1 : Demography and anthropometry of study subjects.

Characteristics	Observed values[n=552]
Age,[mean(+SD),years]	9.7±2.3
Gender Male, n(%) Female, n(%)	311(56.3) 241 (43.7)
Height,[mean(+SD),cm]	109.0±16.4
Weight,[mean(+SD),kg]	23.8±6.0

Table 2 shows no significant difference in demographics and clinical history in SCA subjects based on the presence or absence of PHT.

Table 2: Comparison of demography and clinical history of subjects with and without PHT.

Characteristics	PHT[n=113]	No PHT [n=439]	test statistics	p value
Age[mean(±SD),years]	10.8±2.2	9.4±2.3	t test=5.7	**0.000****
Male, n(%)	77(66.9)	234 (53.5)	Chi=6.6	**0.010****
Frequency of pack cell transfusion [mean(±SD)]	6.9± 7.4	3.6±6.7	Chi=4.8	**0.000****
Number of crisis[mean (±SD)]	10.5±2.5	4.6±1.9	Chi =3.6	**0.000****
Duration of Hydroxyurea therapy[mean(±SD) weeks]	94.7±59.7	134.1±59.7	t test= -1.1	**0.023****

Table 3 shows the clinical findings in SCA patients with and without PHT. The presence of jaundice, parasternal heave, splenomegaly and a loud component of the second heart sound differed significantly between SCA subjects with and without PHT. Splenomegaly, parasternal heave and loud second heart sound were noted more commonly among SCA subjects with PHT.

Table 3 :Comparison of Clinical abnormalities of subjects with and without PHT.

Clinical findings	PHT [n=113]	No PHT [n=439]	Test statistics	p value
Height,[mean(±SD),cm]	115.5(17.2)	107.3(15.8)	t test=4.5	**0.000****
Weight,[mean(±SD),kg]	26.9(5.8)	22.9(5.8)	t test=6.4	**0.000****
Jaundice	30 (26.5%)	152 (34.6%)	Chi=3.1	0.078
Digital clubbing	3 (2.6%)	3 (0.6%)	Chi=3.1	0.077
Parasternal heave	27 (23.4%)	15 (3.4%)	Chi=52.0	**0.000****
Loud second heart sound	58 (50.4%)	68 (15.5%)	Chi=62.8	**0.000****
Haemic murmur	31 (2.6%)	67 (15.3%)	Chi=8.4	**0.004****
Splenomegaly	30 (26.0%)	40 (9.1%)	Chi=23.5	**0.000****
Hepatomegaly	70 (60.8%)	270 (61.7%)	Chi=0.03	0.857

Table 4 shows the laboratory characteristics of SCA subjects with and without pulmonary hypertension.

Table 4 : Comparison of laboratory parameters of SCA subjects with and without PHT

Lab. Characteristics	PHT [n=113]	No PHT[n=439]	t-test statistics	df*	p value	95% CI
Haemoglobin [mean±SD(g/dl)]	6.4±(1.4)	7.5±(4.8)	-3.9	545.446	**0.021****	-1.5 to -0.5
Reticulocyte count [mean ±SD(%)]	8.2±(1.6)	5.0±(0.8)	20.5	130.892	**0.000****	2.8 to 3.5
Fetal haemoglobin [mean ±SD(%)]	17.0±(6.7)	18.6±(6.2)	-2.3	168.559	**0.021****	-2.9 o -2.5

*df- degree of freedom;** p value <0.05 is considered to be statistically significant, CI- Confidence interval

In order to control for confounders, multivariate analysis by logistic regression was carried out on these variables to identify independent associations of PHT in SCA subjects. The independently associated variables and their Odds Ratios are shown in (Table 5).

Table 5 : Independent variables associated with PHT

Clinical findings	Odds ratio	95% CI	p-value
Hepatomegaly	0.962	0.63-1.46	0.857
Splenomegaly	3.503	2.06-5.94	**0.000****
Jaundice	0.662	0.41-1.04	0.078
Loud second heart sound	5.522	3.52-8.64	**0.000****
Parasternal heave	8.63	4.41-16.89	**0.000****
Digital clubbing	3.87	0.77-19.45	0.077
Haemic murmur	2.03	1.25-3.31	**0.004****

CI = Confidence Interval

Our study consist of a total 552 enrolled patients of sickle cell disease out of which 311 were male and 241 were female making male to female sex ratio of (1.29 :1). Overall prevalence of pulmonary hypertension in our study was 20.4%. Of these, 6.5% patients have mild pulmonary hypertension and 14% patients have moderate pulmonary hypertension and 79.5% patients have normal pulmonary pressure. None of the participants had severe pulmonary hypertension. (Table 6)

Table 6 :Severity of pulmonary hypertension in subjects

Severity	Mild	Moderate	Severe	Normal
n(%)	36(6.5)	77(14)	0(0)	439(79.5)

Table 7 shows 37.2% sickle cell children with pulmonary hypertension were of age group less than 10 years and 62.8% were of age group of more than 10 years.

Table 7: The Age correlation of PHT in subjects

Age group	With PHT n (%)	Without PHT n (%)
5-10 years	42 (37.2%)	288 (65.6%)
>10 years	71 (62.8%)	151 (34.4%)

Discussion

During the study period a total of 552 cases of sickle cell anaemia were enrolled as the study subjects excluding 55 drop outs. Among them 56.3% were male children and 43.7% were female with male to female ratio of 1.29 : 1.

Prevalence of pulmonary hypertension among sickle cell anaemia in our study was 20.4% which was similar to figures reported by Ambrusko et al [13] and Colombati et al [14].

Table 8:The prevalence rates in children in different studies

Year	Authors	Age group(years)	Prevalence (%)
2008	Pashankar et al	6-14	30
2008	Minniti et al	3-20	11
2009	Sedrak et al	Mean age 12	8.3
2009	Dham et al	3-20	11
2009	Margaret et al	5-19	20
2010	Dahoui et al	6-13	31.8
2016	Patel et al	5-18	38
2016	Allawi et al	3-3920.2	20.2
2017	Sokunbi et al	5-18	22.9

Sickle cell disease patients with pulmonary hypertension presented at late age 10.8±2.2 years as compared to those who had normal pulmonary hypertension 9.4±2.3 years. Three years of age was the youngest age studied and at which pulmonary artery hypertension was found in studies by Minniti C.P. et.al & Colombatti R et. al. [15,16]. Since the mean age of developing pulmonary hypertension in our study was more, larger studies are required to comment on earliest age for screening children with sickle cell anemia for pulmonary hypertension.

In our study the prevalence of PHT increased with age in children with SCA in steady state. This is consistent with the findings of Minniti *et al.*[15] Colombatti *et al.* [14] and Dosunmu *et al.*[16] in the USA, Italy and Nigeria respectively in which the prevalence of PAH also increased with rising age. The finding however contrasts with another Nigerian study conducted on children and adults by Aliyu *et al* [17] where the prevalence of pulmonary hypertension declined with rising age. Pashankar *et al.* [5] in the USA found no correlation between age and increasing pulmonary hypertension in a study involving children and adults.

Males were more frequently affected by PHT than females in the current study which was statistically significance (p = 0.010). A similar study by Rubin LJ showed a significant association with male sex in children 10 years aged or older [18].

It was also observed that SCA children without PHT had higher HbF level than those with PHT and is therefore likely that HbF offers some protection and this difference was statistically significant (p=0.021), but our study was not consistent with the observation made by Sokunbi et al [19] in Lagos, Al- Allawi et al [20] in Iraq and Colombatti et al [14] in Italy. Although HbF is the major genetic modulator of haematologic and clinical features of sickle cell disease, it appears that high level of HbF may not completely protect against PHT in children with SCA. This is unclear and will require further studies.

Our study shows a significant, positive correlation between SCA children with PHT and reticulocyte count and previous studies also emphasized the important role of haemolysis as a significant contributor to PHT [11,21]. These inferences have been drawn from findings of decreased haemoglobin with an associated increase in markers of haemolysis such as reticulocyte count. Therapies aimed at decreasing haemolysis have been postulated as measures to prevent occurrence of and delay progression of PHT in children with SCD [22].

Certain clinical abnormalities like parasternal heave, loud second heart sound, haemic murmur and splenomegaly are statistical significantly associated with PHT and jaundice, digital clubbing, hepatomegaly are not statistically significant. Previous study by Sokunbi et al [19] features like jaundice, parasternal heave, loud second heart sound and hepatomegalywere statistically significant and hence more studies required to establish the correlation of such clinical features with PHT.

The correlation between PHT in children with SCA and haemoglobin though weak, was statistically significant (p=0.021) and similar to observations made by Aliyu ZY et al [17] and Ambrusko SJ et al [13] and Liem RI et al [22]. Some previous studies have pointed out that PHT in children with SCA likely to be enhanced in severely anaemic patients with high stroke volume and increased cardiac output [23,24].

Following variables in treatment were found significant amongst children with pulmonary hypertension. Frequency of packed cell transfusion required in children with pulmonary hypertension was 6.9 ± 7.4 as compared to 3.6 ± 6.7 in those without pulmonary hypertension which was statistically significant. Our study findings are in consistent with the observation made by Hagar et al [25]. This suggests that better management of haemolytic crisis plays an important role in manifesting complications. Increased number of crisis in lifetime associated with PHT which is statistically significant, a similar observation was made by Patel et al [26]. Our study also reveals statistically significant(p value=0.023) relationship between the duration of use of hydroxyurea and occurrence of PHT which was not in consistent with previous study by Sokunbi et al [19]. So we can conclude that longer duration of use of hydroxyurea may give some protection against PHT. However further studies are required for more analysis.

In our study demographically 59.7% of patients were of age group between 5 to 10 years and 40.1% were of age group more than 10 years. Out of all sickle cell children with pulmonary hypertension, 37.2% were of age group less than 10 years and 62.8% were of age group of more than 10 years. Association between these age groups and occurrence of pulmonary hypertension were statistically significant. Previous study by Patel et al had observed 36.8% of pulmonary hypertension in children with sickle cell

anaemia were between 5 to 10 years of age and 63.2% of pulmonary hypertension were more than 10years of age [26].

In the same study by Patel et al [26], 24% of children with SCA had mild pulmonary hypertension and 14% had moderate pulmonary hypertension, but in our study we have 6.5% patients have mild pulmonary hypertension and 13.9% patients have moderate pulmonary hypertension.

Limitations of the Study

It is an observational study where causal relation could not be established. A larger sample may yield more reliable results.

It is being a hospital based study which could have included some patients with acute illnesses; inclusion of only steady state sickle patients could have yielded a more reliable results.

There are increased chances of involvement of bias in the study like recall bias & reporting bias, a form of information bias.

Here non-random sampling is used but random sampling technique is a better option, as selection bias could not be prevented in non random sampling.

Confounder and effect modifier could not be adjusted at the stage of design and analysis level.

Ethical Approval

Written informed consent was obtained from all participants before study. Participants were assured of complete voluntary participation, and medical care was not affected by the choice of participation in the study. All data were be coded, and privacy was be maintained during data collection to achieve strict confidentiality. Ethical approval was allowed by VIREC(VIMSAR Institutional Research And Ethics Committee) vide approval no. 129/19-I-S-130/Dt.25.01.2019.

Conclusion

The aim of our study was to contribute new insight to the area of prevalence of pulmonary arterial hypertension among children of sickle cell anaemia in Western Odisha. It was also aimed to compare the prevalence of pulmonary arterial hypertension among children with sickle cell anaemia in our study place to the rest of country. The results of our study showed the prevalence of pulmonary arterial hypertension in children with sickle cell anaemia age group between 5-14 years is 20.4 %. Pulmonary arterial hypertension is more common in older male children with sickle cell anaemia.

Advancement in diagnostic technology and progress in therapeutic management have improved the life expectancy of pulmonary hypertension in children with sickle cell anaemia in western countries: however, the situation in developing countries like India is quite different. Primary health care centers in India are not adequately equipped to detect pulmonary hypertension. Spreading awareness and improving the method at primary health care level may ameliorate this.

Further prevalence of pulmonary hypertension among sickle cell anaemia children varies in wide range depending upon the population and diagnostic tool. For better estimation of prevalence, more elaborate community based studies that include echocardiography as well as examination of children with sickle cell anaemia are needed.

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