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Original Research Article

Prevalence of pulmonary hypertension in pediatric patients with beta-thalassemia major in Central India: a cross sectional study

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ABSTRACT

Background: The objective of the study was to determine the prevalence of pulmonary hypertension in pediatric patients with beta thalassemia major in a tertiary care centre in Central India.
Methods: A cross sectional study was conducted in department of pediatrics, Government Medical College and Hospital, Nagpur, India over a period of 2 years. Total 100 subjects of thalassemia major diagnosed by high performance liquid chromatography (HPLC) attending day care in this department were enrolled for study. Measurement of pulmonary pressure was done by using 2D echocardiography with Doppler studies and tricuspid regurgitant jet velocity was measured. This was done by experienced cardiologist. Variables predictive of pulmonary hypertension studied were age, sex, serum ferritin levels, age of onset of chelation therapy, compliance to chelation therapy and number of blood transfusion per year.
Results: Out of 100 subjects, 18 subjects had pulmonary hypertension. Univariate analysis proved that age, serum ferritin levels, age of onset of chelation therapy, compliance to chelation therapy and number of blood transfusion per year were significant predictors of pulmonary hypertension. While, multiple logistic regression analysis revealed that only 3 variables that is age of onset of chelation therapy, number of blood transfusion per year and compliance to chelation therapy retained their significance in this patient population.
Conclusions: Prevalence of pulmonary hypertension was found out to be 18%. 2 subjects in the pulmonary hypertension group died. High morbidity and mortality of pulmonary hypertension clearly indicates that much work is needed in disease detection and development of more effective therapies. For thalassemic children, early detection and prevention of pulmonary hypertension in childhood would improve survival, reduce morbidity and mortality.

Keywords: Pulmonary hypertension, Beta thalassemia, TR jet velocity

INTRODUCTION

Beta-thalassemia is one of most common autosomal recessive disorders worldwide. It is the commonest single-gene disorder in the India.[1] Thalassemia major is characterized by ineffective hemoglobin synthesis with resultant chronic hemolysis. Although prevalent in Mediterranean countries and in the Middle East, this disease has become a global health related problem due to increased immigration trends.[2] Pulmonary hypertension (PH) is a disease of the pulmonary vasculature characterized by elevated pulmonary artery pressure and pulmonary vascular resistance. It is typically progressive, leading to right ventricular overload and eventually to right ventricular failure and premature death.[3,4] The increase in pulmonary vascular resistance is related to a number of progressive changes in the pulmonary arterioles, including: vasoconstriction, inflammation, in-situ thrombosis and proliferative remodeling of the pulmonary vessel wall.[5] Also, it is related to tissue hypoxia leading to endothelial dysfunction and high output state due to anemia. Lastly, oxidative tissue damage secondary to iron

overload may result in pulmonary vascular remodeling and increased vascular resistance.[2]

The aim of the study was to define the prevalence of pulmonary hypertension in pediatric patients with thalassemia major; and to identify the variables predictive of pulmonary hypertension, including treatment modalities such as transfusion rates or chelation therapy.

METHODS

A cross sectional study was conducted at department of pediatrics, Government Medical College and Hospital, Nagpur, India over a period of 2 years from July 2018 to June 2020. Diagnosed cases of thalassemia major by high performance liquid chromatography (HPLC) who were attending day care in this department were evaluated based on selection criteria. Patients with beta thalassemia intermediate and other hemoglobinopathies, abnormal systolic or diastolic left ventricular function, HIV positive patients and patients not willing to participate were excluded from the study. After ethical clearance from institutional ethical committee, all subjects fulfilling inclusion criteria were enrolled. Proper history such as regarding drug (chelation therapy), age at diagnosis, status and compliance to chelation therapy and details of transfusion were obtained. Data was collected using structured data collection sheet. The upper limit for pulmonary artery systolic pressure was estimated to be TR jet velocity of 2.5 m/s (250 cm/s) in the absence of pulmonary stenosis.[6] After enrollment of study subjects, they were divided into 2 groups according to the values of TR jet velocity so obtained (a) group I- TR jet velocity>250 cm/sec; and (b) group II- TR jet velocity<250 cm/sec

Sample size was calculated by following method:

$$N = \frac{z^2(1-p)pq}{d^2} = 100,$$

where absolute precision (d) (%)=8, desired confidence level (1-α) (%)=95, z=1.96, and required sample size=100

Measurement of pulmonary pressure was studied by using 2D echocardiography with Doppler studies. Tricuspid valve interrogation was performed using continuous Doppler in apical four chamber or parasternal short axis views and maximal tricuspid regurgitant jet velocity was recorded. Serum ferritin level was used as a surrogate marker for iron overload and chelation therapy efficacy.

Statistical analysis

Considering the expected prevalence of pulmonary hypertension in patients with beta thalassemia major to be 18.5%, with absolute precision of 8% , considering desired confidence level (1-α) being 95%, the sample size was found to be 100.

Collected data was entered on Microsoft excel spreadsheet and data was analyzed in statistical software Stata, version 10.1,2011. Variables were presented as mean±SD for quantitative variables using descriptive statistics. Association between Pulmonary hypertension and age group was calculated by using chi square test. Comparison of mean TR jet velocity with different age group of the subjects and with compliance to chelation therapy were calculated using One-way ANOVA test. Association between pulmonary hypertension and sex was calculated by Pearson chi square test. Significance between number of pulmonary hypertension and compliance to chelation therapy was found out by chi square test. Binary multiple logistic regression analysis was performed to find predictors of pulmonary hypertension adjusting for role of other variables with help of odds ratio. P value<0.05 was considered as statistically significant.

RESULTS

Pulmonary hypertension was seen in 18 subjects out of 100 subjects with prevalence of 18% with confidence interval (95%) being 11.03-26.95%. Pulmonary hypertensive subjects had mean age of 9.69±1.85 years and that of 6.04±2.86 years in those without pulmonary hypertension. Association can therefore be said significant with the p value of 0.0001 (Table 1). Mean TR jet velocity of 128.62±19.12 was recorded in age group of 1-3 years, 176.50±126.62 in 3-5 years, 171.55±62.38 in 5-8 years and 205.87±91.57 in age group of 8-12 years. So, it can be said that prevalence of pulmonary hypertension increases with increasing age. The study revealed that 20% of the males and 15.56% of the females had pulmonary hypertension. It means that pulmonary hypertension is more prevalent in male children as compared to female children although the difference is not statistically significant (Table 2). In patients with pulmonary hypertension, mean value of serum ferritin came out to be 1338.36±425.64 ng/ml and that came out to be 1059.03±394.69 ng/ml in patients without pulmonary hypertension. The difference is statistically significant with p value of 0.0086 (Table 3). It means that higher serum ferritin levels were found in pulmonary hypertensive patients. As serum ferritin level is a good marker of iron overload, we can say that iron overload is an important risk factor for developing pulmonary hypertension. Subjects with pulmonary hypertension received 14±4.86 blood transfusion/year and that without pulmonary hypertension received 11.2±2.5 blood transfusion/year. The difference is statistically significant with the p value of 0.0007 (Table 4).

Thus, the patients who received more frequent blood transfusion were at risk of pulmonary hypertension. Subjects with pulmonary hypertension started chelation therapy at significantly later age (5.6 years) as compared to those subjects without pulmonary hypertension (3.8 years), that is, almost 2 years late. The difference was found out to be statistically significant with p value of 0.0001 (Table 5). The subjects who were on regular therapy had mean TR jet velocity of 165.34±62.18 cm/sec.

Subjects who were on intermittent therapy had mean TR jet velocity of 216.90±133.15 cm/sec.

Comparison was found out to be significant with p value of 0.0203 (Table 6). The subjects who were on regular therapy had mean TR jet velocity of 165.34±62.18 cm/sec. Subjects who were on intermittent therapy had mean TR jet velocity of 216.90±133.15 cm/sec. Comparison was found out to be significant with p value of 0.0203 (Table 6).

2 subjects died during study duration. Both these patients had high TR jet velocity (416 cm/sec and 392 cm/sec respectively). Significant association was found out with p value of 0.003 (Table 8).

Table 1: Association between pulmonary hypertension and age (years).

Pulmonary hypertension	Mean	SD
Yes	9.69	1.85
No	6.04	2.86
P value	0.0001 (S)	

Note: S- significant.

Table 2: Association between pulmonary hypertension and sex.

Sex	Pulmonary hypertension			
	Yes		No	
	N	%	N	%
Male	11	20	44	80
Female	7	15.56	38	84.44
Total	18	100	82	100

Note: Pearson Chi 2 (1) 0.3312, p=0.565 (NS), NS- not significant.

Table 3: Association between pulmonary hypertension and serum ferritin (ng/ml).

Pulmonary hypertension	Mean	SD
Yes	1338.36	425.64
No	1059.03	394.69
P value	0.0086 (S)	

Note: S-significant.

Table 4: Association between pulmonary hypertension and number of blood transfusion per year.

Pulmonary hypertension	Mean	SD
Yes	14	4.86
No	11.2	2.5
P value	0.0007 (S)	

Note: S-significant.

Table 5: Association between pulmonary hypertension and age of onset of chelation therapy (years).

Pulmonary hypertension	Mean	SD
Yes	5.61	1.24
No	3.79	1.34
P value	0.0001 (S)	

Note: S-significant.

Table 6: Comparison of mean TR jet velocity by compliance in chelation therapy.

Compliances	Mean	SD
Regular (n=61)	165.34	62.18
Intermittent (n=31)	216.90	133.15
Not stated (n=8)	146.88	17.66
Total (n=100)	179.85	91.57
P value (by One-way ANOVA)	p=0.0203 (S)	

Table 7: Comparison of pulmonary hypertension patients with compliance to chelation therapy.

Compliance	N	Pulmonary hypertension	%
Regular	61	8	13.11
Intermittent	31	10	32.26
Not stated	8	0	0.00
Total (by Chi square test)	100	18	18.00

P value (by Chi square test); p=0.030, significant.

Table 8: Association between mortality and pulmonary hypertension.

Death	Pulmonary hypertension			
	Yes		No	
	N	%	N	%
Yes	2	100	0	0
No	16	16.33	82	83.67
Total	18	100	82	100
Pearson Chi^2 (1)=8.7003	p=0.003 (S)			

Table 9: Predictors of pulmonary hypertension (adjusting for role of other variables) from multiple logistic regression analysis.

Pulmonary hypertension	Odds ratio	95% confidence interval	P value
Age (>5 years)	2.97	0.34-26.21	0.327
Gender	0.78	0.19-3.14	0.723
Serum ferritin	1.00	0.99-1.02	0.114
No. of blood transfusion	1.28	1.03-1.59	0.028
Age of onset of chelation therapy (years)	3.69	1.79-7.61	0.001
Compliance to chelation therapy	35.20	3.32-372.94	0.003

Multiple logistic regression analysis shown in Table 9 reveals only three predictors were found to retain their significant contribution to increased prevalence of pulmonary hypertension; no. of blood transfusion per year (p value=0.028), age of onset of chelation therapy (p value=0.001) and compliance to chelation therapy (p value=0.003). Bivariate analyses revealed that 5 factors, that is, age, serum ferritin, no of blood transfusions/year, age of onset of chelation therapy and compliance to chelation therapy are significantly associated with increased prevalence of pulmonary hypertension in patients with beta thalassemia.

DISCUSSION

Management of β thalassemia has been dramatically improved in the last two decades due to better availability of transfusion regimen, iron chelation therapy, proper management of complications and good supportive care, making it possible for a thalassemic child to have a near normal life span, with a good quality of life. However, frequent blood transfusion results in progressive iron overload, which if not adequately treated causes severe complications, including liver, endocrine gland damage and heart dysfunction. One important aspect of management in transfusion dependent β thalassemic patients is early recognition and treatment of cardiac dysfunction. Detection of cardiac complications is important as inexpensive therapy is readily available. Clinically overt manifestations of cardiac complications occur late in life and most of the studies available are done on adults. Only a very few pediatric studies are available, we therefore planned this study with the aim to study prevalence of pulmonary hypertension in children suffering from β-thalassemia major and to evaluate its relation, if any, with age, sex, serum ferritin level, number of blood transfusion per year, age of onset of chelation therapy and compliance to chelation therapy etc. Worldwide prevalence of pulmonary hypertension in β thalassemia major patients varies from 10 to 78.8% (average-30%).[4,7] Pulmonary hypertension was reported 37.5% in Egypt by Beshlawy et al and 75% in Israel by Griseru et al.[8,9]

Variations in results may be due to different methods used to determine pulmonary pressure status, the different ages of the studied patients, difference in treatment protocols including different transfusion rates and chelation therapies. In this study, age of the subject was studied as a predictor of pulmonary hypertension. It was found that as the age increases, risk of pulmonary hypertension increases and there was significant association between pulmonary hypertension and increasing age (p value=0.0001). In this study, it was found that 50% of the subjects were belonging to age group of greater than 8 years who had pulmonary hypertension. Similar observation was made by Du et al where most of the patients of older age group (66%) had pulmonary hypertension and Results contrary to this study was shown by Goksel Kiter et al where prevalence of pulmonary hypertension in older age group was found to be only 6%.[10,11] In present study, among the 18 subjects with pulmonary hypertension, there were 11 (61.11%) males and 7 (38.89%) females with no significant difference in the frequency of pulmonary hypertension between boys and girls (p value=0.565). Similar observation was made in the study done by Alkholy et al in which it was found that in pulmonary hypertensive patients, 65.5% were males and 34.5% were females with no significant difference in frequency of pulmonary hypertension between males and females (p value=0.722).[12] In present study, all subjects received multiple transfusions per year (mean±SD=11.71±3.21). The mean Serum ferritin level was 1109.31±412.56 ng/ml, values ranged between 430-2090 ng/ml. Serum ferritin was used as surrogate marker for assessment of iron status in these patients, and present study revealed significant association between serum ferritin level and pulmonary hypertension (p value=0.0086). This finding suggested possibility that serum ferritin level which was the indicator of chronic iron exposure, plays important role in developing pulmonary hypertension. The mean serum ferritin came out to be 1338.36±425.64 in patients with pulmonary hypertension and 1059±394.69 in patients without pulmonary hypertension in this study.

Similar observation were reported by Du et al in which it was found that higher ferritin levels was found in 75% of the subjects with pulmonary hypertension.[10] Study by Elafy et al also showed significantly higher level of serum ferritin level in patients with pulmonary hypertension as compared to patients without pulmonary hypertension.[13] In this study, there was significant association found (p value=0.0007) between pulmonary hypertension and

number of blood transfusion per year. The mean number of blood transfusion per year was 14±4.86 in patients with pulmonary hypertension and 11.2±2.5 in patients without pulmonary hypertension. This may indicate that frequency and amount of blood transfusion may be more important parameter to predict the development of pulmonary hypertension. Similar observation was reported in the study by Du et al in this, subjects with pulmonary hypertension had blood transfusion rates of 17 per year suggestive of risk of pulmonary hypertension is greater in subjects receiving frequent blood transfusion which is similar to our study.[10] In this study, out of 100 thalassemia patients, 91 subjects (91%) were on chelation therapy and all were on single oral iron chelator, deferasirox (@20 mg/kg/day) once daily. Other 9 patients (9%) were not eligible for the criteria of starting of chelation therapy according guidelines by Thalassemia International Federation (2008) which advises that iron chelation should be started after 10-15 transfusions or when the serum ferritin levels are above 1000 ng/ml 100).

Thalassemia children with pulmonary hypertension started chelation therapy at significantly later age (5.6 years) as compared to those without pulmonary hypertension (3.8 years), that is, almost 2 years late (p value=0.0001).Study done by Vlahos et al found that pulmonary hypertension was seen in subjects whose age of onset of chelation therapy was at later age which was similar to our study, that was, 7.28±1.0 years and that was 3.08±1.7 years in subjects without pulmonary hypertension.[2]

From our study, we can say that subjects whose compliance to chelation therapy was not good that is, who received intermittent chelation therapy had TR jet velocity on higher side, mean value of TR jet velocity being 216.90±133.15 cm/sec as compared to those who were on regular chelation therapy, mean value of TR Jet velocity being 165.34±62.18 cm/sec. Difference was found out to be statistically significant with p-value of 0.0203. Similar finding was observed in the study done by Aessopos et al in which it was found that no pulmonary hypertension was seen in subjects with good compliance to chelation therapy.[14]

During the study period, there were 2 deaths out of 18 subjects whose TR jet velocity was greater than 250 cm/sec. It can be compared with the study done by Du et al in which 2 out of 33 subjects (6.06%) died who were diagnosed to have pulmonary hypertension.[10] In our study, Bivariate analyses revealed that all 5 factors, that is, age, serum ferritin, no of blood transfusions/year, age of onset of chelation therapy and compliance to chelation therapy are significantly associated with increased prevalence of pulmonary hypertension in patients with beta thalassemia. Also, multiple logistic regression analysis was performed for predictors of pulmonary hypertension adjusting for role of other variables revealed only three predictors were found to retain their significant contribution to increased prevalence of pulmonary hypertension i. e.; no. of blood transfusions/year, age of onset of chelation therapy and compliance to chelation therapy.

Limitations

Three limitations of the study should be acknowledged (a) it included a relatively small sample size, although this can be explained by the nature of the this study, describing the experience of a single centre, (b) we used serum ferritin levels as a surrogate for iron overload and chelation therapy efficacy. Despite its widespread use, this parameter provides only a rough estimation and has been shown to be inferior compared to cardiac magnetic resonance-derived values, and (c) right heart catheterization was not performed due to lack of feasibility at our centre.

CONCLUSION

Prevalence of pulmonary hypertension was found out to be 18%. Doppler echocardiography can identify this abnormality and is helpful in assessment of pulmonary hypertension. Instead of waiting till pulmonary hypertension occurs, efforts at identifying patients at greater risk of disease and prevention of pulmonary hypertension should be undertaken. Pediatric care provider should be sensitized for this potentially fatal complication, its proper management and follow up of beta thalassemia children specially who are at high risk. Until more comprehensive data regarding diagnostic evaluation, natural history and response to therapy of thalassemia patients with pulmonary hypertension are available, sustained research efforts are imperative to develop best practices in this vulnerable patient population.

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REFERENCES

1. Grow K, Vashist M, Abrol P, Sharma S, Yadav R. Innovare Academic Sciences beta thalassemia in India. Current Status Challenges Ahead. 2014;6(4):2-7.
2. Vlahos AP, Koutsouka FP, Papamichael ND, Makis A, Baltogiannis GG, et al. Determinants of pulmonary hypertension in patients with Beta-thalassemia major and normal ventricular function. Acta Haematol. 2012;128(2):124-9.
3. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation. 2006;114(13):1417-31.
4. Aessopos A, Farmakis D, Deftereos S, Tsironi M, Tassiopoulos S, Moyssakis I, et al. Thalassemia heart disease: A comparative evaluation of thalassemia major and thalassemia intermedia. Chest. 2005;127(5):1523-30.
5. Meloni A, Detterich J, Pepe A, Harmatz P, Coates TD, Wood JC. Pulmonary hypertension in well-

transfused thalassemia major patients. Blood Cells Mol Dis. 2015;54(2):189-94.
6. Walker M, Wood J. Cardiac complications in thalassaemia major. In: Cappellini MD, Cohen A, Porter J, eds. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd ed. Nicosia (CY): Thalassaemia International Federation; 2014.
7. Aessopos A, Farmakis D. Pulmonary hypertension in beta-thalassemia. Ann N Y Acad Sci. 2005;1054:342-9.
8. Beshlawy A, Youssry I, El-Saidi S, El Accaoui R, Mansi Y, Makhlouf A, et al. Pulmonary hypertension in beta-thalassemia major and the role of L-carnitine therapy. Pediatr Hematol Oncol. 2008;25(8):734-43.
9. Grisaru D, Rachmilewitz EA, Mosseri M, Gotsman M, Lafair JS, Okon E, Goldfarb A, Hasin Y. Cardiopulmonary assessment in beta-thalassemia major. Chest. 1990;98(5):1138-42.
10. Du ZD, Roguin N, Milgram E, Saab K, Koren A. Pulmonary hypertension in patients with thalassemia major. Am Heart J. 1997;134(3):532-7.
11. Kiter G, Balci YI, Ates A, Hacioglu S, Sari I. Frequency of pulmonary hypertension in asymptomatic beta-thalassemia major patients and the role of physiological parameters in evaluation. Pediatr Hematol Oncol. 2010;27(8):597-607.
12. Alkholy UM, Mohamed SA, Elhady M, Attar SE, Abdalmonem N, Zaki A. Vascular endothelial growth factor and pulmonary hypertension in children with beta thalassemia major. J Pediatr (Rio J). 2019;95(5):593-9.
13. Elalfy MS, Youssef OI, Deghedy MMR, Abdel Naby MM. Left Ventricular Structural and Functional Changes in Children With β-Thalassemia and Sickle Cell Disease: Relationship to Sleep-disordered Breathing. J Pediatr Hematol Oncol. 2018;40(3):171-7.
14. Aessopos A, Farmakis D, Hatziliami A, Fragodimitri C, Karabatsos F, Joussef J, et al. Cardiac status in well-treated patients with thalassemia major. Eur J Haematol. 2004;73(5):359-66.

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