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PULMONARY FUNCTION TESTS IN CHILDREN WITH BETA THALASSEMIA AND ITS CORRELATION WITH IRON OVERLOAD

Medicine

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ABSTRACT

Iron overload is the principal determinant of major complications in conditions requiring repeated blood transfusions, like Beta Thalassemia Major and Sickle Cell Anemia. Although pulmonary dysfunction is not the most significant clinical manifestation of thalassemias, or indeed does not produce any symptoms, a certain reduction of pulmonary volumes has been reported to occur in most subjects with beta thalassemia receiving regular blood transfusions. This study was done to assess the pulmonary function of such patients by Spirometry and the type of pulmonary dysfunction and to study its co-relation with iron overload. A total of 54 patients with Beta Thalassemia major on regular blood transfusions, of ages 6 years and above, were made to undergo Pulmonary Function Tests, of which 21 (38.89%) were females and 33 (61.11%) were males. Serum Ferritin values were recorded in all patients as a measure of iron overload. Pulmonary dysfunction was observed in 42 (77.78%) patients.`A predominantly restrictive pattern was found in 38 (90.48%) patients. An obstructive pattern was found in 4 (9.52%) patients. Patients with an FEV1/FVC ratio of less than 70% of the predicted value were labeled as having obstructive pulmonary dysfunction. Patients with FVC values of less than 80% of the predicted value and a FEV1/FVC ratio of more than 80 percent of th6e predicted value were labeled as having restrictive pulmonary dysfunction . Among patients with restrictive dysfunction, those having FVC values between 70-79%, 50-69% and 35 to 49% were graded as having mild, moderate and severe restrictive dysfunction respectively. Among subjects with obstructive dysfunction, those having FEV1/FVC ratio values between 70-79%, 50-69% and 35-49% were graded as having mild, moderate and severe obstructive dysfunction respectively. The number of patients with mild, moderate and severe pulmonary dysfunction were 13 (30.95%), 25 (59.52%) and 4 (9.52%) respectively. The mean ferritin value was calculated for each category of severity to see if any kind of correlation exists between pulmonary dysfunction and iron overload. Pulmonary dysfunction was found in a significant majority of the patients, however no significant correlation was found between severity of pulmonary dysfunction and iron overload.

KEYWORDS

INTRODUCTION

Every year around 15,000 infants are born with hemoglobinopathies in India. Among all the hemoglobinopathies Beta-thalassemias are the major cause of serious health problems. India accounts for 10 percent of the total world Thalassemia population. Beta Thalassemia major is characterised by Intramedullary hemolysis which leads to Ineffective erythropoiesis. This results in Severe Anemia, requiring repeated Blood Transfusions.. The survival of patients with B-Thalassemia major has improved considerably with blood transfusionst.Iron overload is the principal determinant of major complications in conditions requiring repeated blood transfusions, like Beta Thalassemia Major and Sickle Cell Anemia. Every unit of erythrocytes that is transfused , contains 200-250 mg of iron as a component of the red heme pigment.

Post mortem studies have shown the presence of iron deposition in lungs of thalassemia major patients. Bronchoalveolar lavage was done in thalassemic patients with abnormal PFTs and iron laden macrophages were detected. The results suggested that iron plays a major role in the etiopathogenesis of these abnormalities. Reduction of pulmonary volumes has been reported to occur in most subjects with beta thalassemia but the pathophysiology is less clearly understood. Studies have shown that the Alveolar Capillary membrane is the predominant site of lung involvement. This excessive iron deposition in lungs causes repiratory dysfunction. Restrictive abnormalities are the most frequent, being reported in up to 80 percent of patients in some of the studies and diffusion impairment has been the commonest impairment of lung function. Numerous studies have been carried out on the effects of iron deposition in the heart and liver but the studies on pulmonary function of patients in thalassemia major have been few. This study was done to assess the pulmonary function of such patients and the type of pulmonary dysfunction that develops (obstructive/ restrictive) so that spirometry is included as a necessary screener in all children with beta thalassemia major in order to prevent the sequelae of pulmonary disease. This study also tried to see if a significant correlation between the pulmonary dysfunction and iron overload exists.

AIMS AND OBJECTIVES

The aim of this study was to assess the pulmonary functions of children with BetaThalassemia major using Spirometry and to correlate the pulmonary dysfunction with iron overload (Serum Ferritin values).

METHODOLOGY

A prospective hospital based study. This study was conducted in the Thalassemia unit of Christian Medical College and Hospital. Out of 84 patients with Beta Thalassemia Major, 56 patients were aged 6 years and above. Two patients were excluded from the study due to Chronic liver disease. A total of 54 patients were recruited after satisfying the inclusion and exclusion criteria and getting clearance from the Institutional Ethical Committee. **Computerised Spirometry (PRODUCT : SPIROBANK-G ; MODEL : MIR)** was used to assess pulmonary function. Patients with FEV1/FVC ratio < 80% of the predicted value were classified as Obstructive pulmonary dysfunction. Patients with6 FVC < 80 % of predicted value, with FEV1/FVC > 80 % of predicted value were classified as Restrictive pulmonary dysfunction. Patients with FVC values between 70-79%, 50-69% and 35 to 49% were graded as having mild, moderate and severe restrictive dysfunction respectively. Patients with FEV1/FVC ratio values between 70-79%, 50-69% and 35-49% were graded as having mild, moderate and severe obstructive dysfunction respectively. Criteria for classifying the pattern of pulmonary dysfunction and its severity were taken from the study done by Boddu et al (7). The mean ferritin value was calculated for each category of severity to see if any kind of correlation exists between pulmonary dysfunction and iron overload. An average of the last three ferritin levels measured for each patient was taken as an indicator of their iron overload. All children above the age of 6 years with Beta Thalssemia Major, undergoing regular blood transfusions (>20) were included in the study. Patients already diagnosed with pulmonary dysfunction (Asthma, Cystic fibrosis, recent acute respiratory tract infections or recurrent pneumonia), Hepatocellular disease or Congestive Cardiac Failure were excluded from the study.

RESULTS AND ANALYSIS

A total of 54 patients were included in this study after meeting the inclusion criteria. All 54 subjects were made to undergo Pulmonary Function Tests. Out of the 54 subjects who underwent PFTs, pulmonary dysfunction was found in 42 (77.78%) subjects while 12 (22.22%) subjects had normal PFTs. Restrictive pattern was observed in 38 (90.48%) subjects with abnormal PFTs while obstructive pattern was seen in only 4 (9.52%) subjects. Out of the 54 subjects, 30 (55.56%) were aged under 10 years. Twenty-five subjects from this age group had pulmonary dysfunction of which 8 (32%) subjects had mild dysfunction, 16 (64%) had moderate dysfunction and 1 (4%) had severe dysfunction. Thirteen (24.07%) patients fell into the age group of 11-15. Eight subjects from this age group had pulmonary dysfunction, of which 2 (25%) had mild dysfunction, 5 (62.50%) had

moderate dysfunction and 1 subject (12.5%) had severe dysfunction. Eleven (20.37%) patients were more than 15 years of age. Nine subjects from this age group had pulmonary dysfunction, of which 3 (33.33%) subjects had mild dysfunction, 4 subjects (44.44%) had moderate dysfunction and 2 (22.22) subjects had severe dysfunction. The number of males were 33 (61.11%) of which 28 (84.85%) had pulmonary dysfunction and females were 21 (38.89%) of which 14 (66.67%) had pulmonary dysfunction. All samples included had undergone atleast 20 or more blood transfusions. Out of the 54 subjects, 43 (79.63%) patients were on Deferasirox for chelation while 11 (20.37%) patients were on deferiprone.

Table 1. Pulmonary dysfunction

Pulmonary dysfunction	Number	Percentage
No	12	22.22
Yes	42	77.78
Total	54	100.00

Table 2. Pattern of pulmonary dysfunction

Pattern	Number	Percentage
Obstructive	4	9.52
Restrictive	38	90.48
Total	42	100.00

Out of the 54 subjects who underwent PFTs, pulmonary dysfunction was found in 42 (77.78%) subjects while 12 (22.22%) subjects had normal PFTs. Restrictive pattern was observed in 38 (90.48%) subjects with abnormal PFTs while obstructive pattern was seen in only 4 (9.52%) subjects.

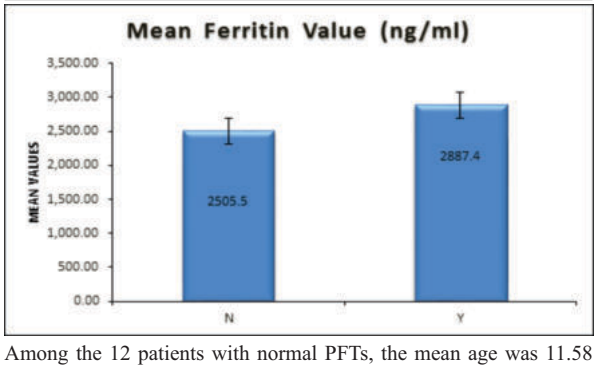
Table 3. Severity of pulmonary dysfunction

Severity	Number	Percentage
Mild	13	30.95
Moderate	25	59.52
Severe	4	9.52
Total	42	100.00

Among the 42 subjects with abnormal PFTs, 13 (30.95%) subjects had a mild dysfunction. Moderate dysfunction was seen in 25 (59.52%) subjects and 4 (9.52%) subjects had severe dysfunction. Out of the 38 subjects with restrictive pattern, 12 (31.58%) subjects had mild dysfunction, 23 (60.53%) subjects had moderate dysfunction and 3 subjects (7.89%) had severe dysfunction. Out of the 4 subjects with obstructive pattern, 1 (25%) subject had mild dysfunction, 2 subjects had moderate dysfunction and 1 (25%) subject had severe dysfunction.

Table 4. Pulmonary dysfunction and Mean Ferritin Value

Pulmonary Dysfunction	No	Yes	P value
AGE (Years)			0.219
Sample size	12	42	
Mean ± Stdev	11.58 ± 3.68	10.17 ± 4.49	
Median	11.5	8	
Min-Max	6-17	6-17	
Mean Ferritin Value (ng/ml)			0.394
Sample size	12	42	
Mean ± Stdev	2505.5 ± 1190.49	2887.4 ± 1169.36	
Median	2401	2451	
Min-Max	487-4630	753-6698	



Among the 12 patients with normal PFTs, the mean age was 11.58 years with a standard deviation of 3.68 and a median of 11.5. The mean ferritin value was 2505.5 ng/ml with a standard deviation of 1190.49.

Among the 42 patients with abnormal PFTs, the mean age was 10.17 years with a standard deviation of 4.49 and a median of 8. The mean ferritin value in this group was 2887.4 ng/ml with a standard deviation of 1169.36, which was higher than the mean ferritin value among the subjects with normal PFTs.

Table 5. Severity of pulmonary dysfunction in relation to mean values of age an

	Severity			
	Mild	Moderate	Severe	P value
AGE (Years)				0.440
Sample size	13	25	4	
Mean ± Stdev	10.15 ± 4.62	9.68 ± 4.31	13.25 ± 5.19	
Median	8	8	15	
Min-Max	6-17	6-17	6-17	
Mean Ferritin Value (ng/ml)				0.472
Sample size	13	25	4	
Mean ± Stdev	3075.69 ± 1246.51	2715.88 ± 1107.03	3347.5 ± 1409.76	
Median	2879	2390	2918	
Min-Max	1871-6698	753-5489	2234-5320	

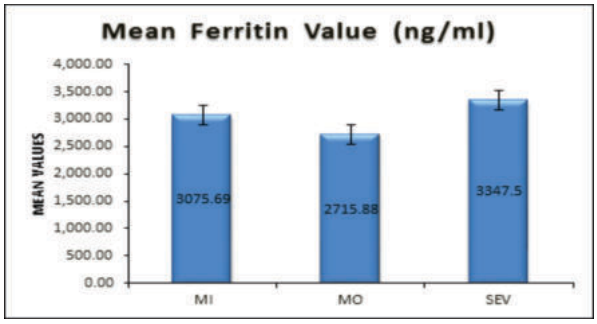
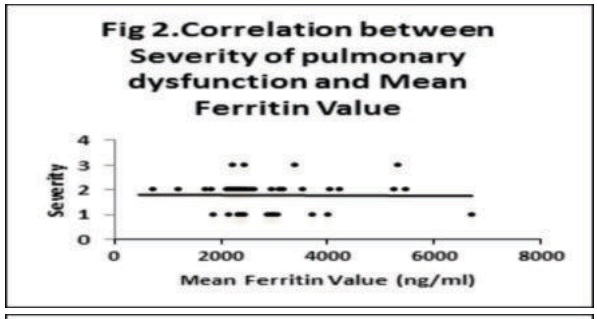
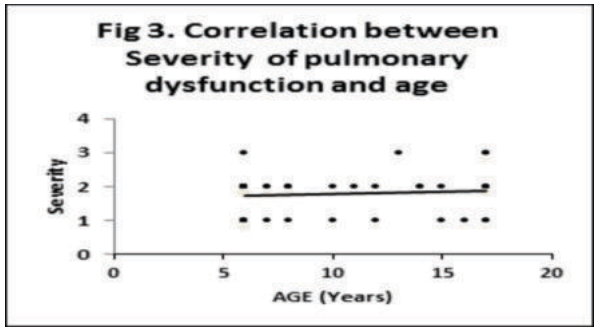


Fig. 1 Severity of pulmonary dysfunction and Mean Ferritin Value

The mean age of subjects with mild disease was 10.15 years with a SD of 4.62. Subjects with moderate dysfunction had a mean age of 9.68 years with a SD of 4.31 and those with severe disease had a mean age of 13.25 years with a SD of 5.19. The mean ferritin value among subjects with mild disease was 3075.69 (SD = 1246.51). Subjects with moderate disease had a mean ferritin value of 2715.88 (SD=1107.03) whereas subjects with severe dysfunction had a mean ferritin value of 3347.5 (SD=1409.76). There was no correlation found between the severity of pulmonary dysfunction and age as well as with Ferritin levels, with p values of 0.440 and 0.472 respectively.





In relation to the severity of pulmonary dysfunction, the Corelation

coefficient for age was 0.087 with a P value of 0.585. No significant correlation was found between severity of pulmonary dysfunction and age. In relation to severity of Pulmonary dysfunction, the mean ferritin value had a correlation coefficient of -0.058 with a P value of 0.7133.

DISCUSSION

Out of the 54 subjects who underwent pulmonary function tests, 42 (77.78%) subjects were found to have pulmonary dysfunction while 12 (22.22%) subjects had normal PFTs(Table 01). Out of the 42 subjects with pulmonary dysfunction, 38 (90.48%) subjects had a restrictive pattern while 4 (9.52%) subjects had an obstructive pattern (Table 02). Thirteen (30.95%) of the 42 subjects with abnormal PFTs had a mild dysfunction. Moderate dysfunction was seen in 25 (59.52%) of these subjects while 4 (9.52%) subjects had severe dysfunction (Table 3). Out of the 38 people with restrictive pattern of pulmonary dysfunction, 12 (31.58%) subjects had mild dysfunction, 23 (60.53%) subjects had moderate dysfunction and 3 subjects (7.89%) had severe dysfunction. Out of the 4 subjects with obstructive pattern, 1 (25%) subject had mild dysfunction, 2 subjects had moderate dysfunction and 1 (25%) subject had severe dysfunction. Moderate pulmonary dysfunction had a higher prevalence in both the groups.

The study showed that a majority of children with beta thalassemia major who undergo transfusion regularly have pulmonary dysfunction. The predominance of restrictive pattern of pulmonary dysfunction is probably due to iron deposition in lungs, leading to lung injury and resulting in a decrease in diffusing capacity. Most studies have shown that the alveolar capillary membrane is the primary site involved in iron deposition in lungs and is the probable reason for restrictive pulmonary dysfunction. Serum Ferritin values were used as an indicator of iron overload in our study. The mean Ferritin value in our study was 2802.54 ng/ml (SD=1173.73). Among the 12 subjects with normal PFTs, the mean Ferritin value was 2505.5 ng/ml (SD= 1190.49) while the 42 subjects with pulmonary dysfunction had a mean ferritin value of 2887.4 ng/ml (SD=1169.36) but the difference in mean ferritin values in both groups was not stastically significant, with a p value of 0.394 (Table 4). Among the 13 subjects with mild pulmonary dysfunction, the mean ferritin value was 3075.69 ng/ml (SD=1246.51). The mean ferritin value of the 25 subjects with moderate dysfunction was 2715.88 ng/ml (SD=1107.03). The mean ferritin value of the 4 subjects with severe pulmonary dysfunction was 3347.5 ± 1409.76. There was no significant correlation between the severity of pulmonary dysfunction and Ferritin values (p = 0.472) (Table 05, Fig1). Of the 54 patients included in this study, 30 (55.56%) were aged 10 years and below. Thirteen (24.07%) patients fell into the age group of 11-15 and 11 (20.37%) patients were more than 15 years of age. The mean age was 10.48 years with a standard deviation of 4.33. Out of the 30 patients aged 10 years and below, 25 (83.33%) had pulmonary dysfunction and 5 (16.67) subjects had normal PFTs. Thirteen subjects were between 11 to 15 years of age, out of which 8 (61.54%) subjects had pulmonary dysfunction and 5 (38.46%) subjects had normal PFTs. There were 11 subjects who were above the age of 15 years. Nine (81.82%) of these subjects had pulmonary dysfunction while 2 (18.18%) subjects had normal PFTs. Among subjects with normal PFTs, the mean age was 11.58 years with a standard deviation of 3.68. The mean age of the subjects with pulmonary dysfunction was 10.17 years with a standard deviation of 4.49. With a p value of 0.219, no stastically significant correlation was found between the age distribution and pulmonary dysfunction. Out of the 30 subjects who were of the age 10 years and below, 25 subjects had pulmonary dysfunction of which 8 (32%) subjects had mild dysfunction, 16 (64%) had moderate dysfunction and 1 (4%) had severe dysfunction. There were 13 patients who were aged between 11 to 15 years. There were 8 subjects from this age group who had pulmonary dysfunction, of which 2 (25%) had mild dysfunction, 5 (62.50%) had moderate dysfunction and 1 subject (12.5%) had severe dysfunction. There were 11 subjects who were above 15 years of age. Nine (81.8%) subjects from this age group had pulmonary dysfunction, of which 3 (33.33%) subjects had mild dysfunction, 4 subjects (44.44%) had moderate dysfunction and 2 (22.22) subjects had severe dysfunction. Moderate pulmonary dysfunction had the highest prevalence in all three age groups. The mean age of the subjects with mild pulmonary dysfunction was 10.15 years (SD=4.62). The mean age of subjects with moderate pulmonary dysfunction was 9.68 years (SD=4.31). Subjects with severe pulmonary dysfunction had a mean age of 13.25 (SD=5.19). The p value was 0.44 and not statistically significant. Much like other studies, no significant correlation was found in our study between pulmonary dysfunction and other variables like gender (p=0.117), weight (p=0.493), height (p=0.695) and the chelating agent used (p=1.00).

CONCLUSION

The results of this study show that there was a significant prevalence of pulmonary dysfunction among children with Beta thalassemia major who are on regular blood transfusions. Restrcitive pattern of pulmonary dysfunction was found to be much more common than obstructive pattern. There were no subjects who had a combined pattern of pulmonary dysfunction. In terms of severity, moderate pulmonary dysfunction was more common as compared to mild or severe dysfunction. Our study found no significant correlation between pulmonary dysfunction and ferritin levels, suggesting that iron overload may not be the primary cause of pulmonary dysfunction in Thalassemic patients. This study was done as there has not been sufficient data on the prevalence of pulmonary dysfunction in Beta thalassemics and no primary cause for pulmonary dysfunction has been established. t. These patients are routinely screened for complications like cardiac, hepatic and endocrine dysfunctions however screening for pulmonary dysfunction has not been included in screening protocols yet. Our study, like most other studies, has proved that there is a significant prevalence of pulmonary dysfunction in such patients and strongly recommends the inclusion of pulmonary function tests as a screening protocol to be done atleast once a year. Patients who are found to have pulmonary dysfunction should further undergo a DLCO test to be evaluated for impairment in diffusion capacity, which has been found to be a common in patients with restrictive pulmonary dysfunction according to most studies.

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