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Original Research Article

Pulmonary function tests in β thalassemia major and its correlation with serum ferritin levels

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ABSTRACT

Background: Extensive studies are conducted on heart, liver and endocrine abnormalities in thalassemia owing to their direct effect on survival, however, lung dysfunction has never been focused upon and is one of the least understood complications in β thalassemia. There's a vacuum for data on pulmonary function tests in β thalassemia major in literature from India. Authors aimed to study pulmonary function and type of abnormality in cases with β thalassemia major above the age of 8yrs and to correlate the result with age and serum ferritin levels.
Methods: Demographic data, hemoglobin value, serum ferritin levels, chelation details and transfusion requirement were analyzed. Spirometry was performed using COSMED pulmonary function test (PFT).
Results: Among the 34 subjects studied, 21 were boys, and 13 were girls. Mean serum ferritin levels of the group was 3610.82±2679.51ng/mL and did not show a significant correlation with age, years of transfusion, and years of chelation. Forced vital capacity (FVC), forced expiratory volume in 1st second (FEV1) % values were lower in boys when compared to girls. PFT showed a restrictive pattern in the study group (FEV1/FVC=>0.7) with significant involvement in 73.5% of cases (FEV1<80%). A statistically significant negative correlation was observed between age and FEV1% (r=-0.577, p=<0.01) highlighting the importance of duration of iron overload. However, there was no significant linear correlation between restrictive lung disease and serum ferritin level (r=-0.06, p=0.75).
Conclusions: Restrictive pattern was the most common abnormality, and it did not correlate with serum ferritin. Pulmonary function monitoring would help in identifying children with significant morbidity and help in initiating an early intervention to improve the quality of life.

Keywords: Ferritin, Pulmonary function, Thalassemia

INTRODUCTION

β-thalassemia major is an inherited, transfusion-dependent chronic anemia which is caused by decreased production of β-globin chains required for formation of hemoglobin. As a result of this free α-chains accumulate in the RBCs and leads to the destruction of majority of the erythroid cells in the bone marrow. Ineffective erythropoiesis, reduced hemoglobin synthesis, and short lifespan of erythrocytes in these patients lead to tissue hypoxemia and severe anemia. This can be partially corrected by maintaining the level of pre-transfusion Hb around 9.5-10.5g/dL by regular blood transfusions.

Owing to their early effect on survival, extensive studies have been conducted on heart and liver dysfunction.

However, lung dysfunction has never been adequately focused upon and remains to be one of the least understood complications. Although it does not produce any symptoms and is not the most significant clinical manifestation of thalassemia, reduction in pulmonary volumes has been reported in most studies conducted in β-thalassemia patients.

Varied abnormalities have been reported and these include restrictive lung disease, obstructive airway disease, impaired diffusing capacity of lung for carbon monoxide (DLCO).[1-7]

However, the physiologic basis of this is still not clearly known and many theories have been put forward by various investigators. Hence authors aimed to study the effect of iron deposition on lungs in children with β thalassemia.

METHODS

A prospective study was conducted from September 2015 to April 2017 in a tertiary care center in India.

Inclusion criteria

- Children in the age group 8-18 years who had been diagnosed with β thalassemia major and were on regular transfusions from the time of diagnosis were recruited into the study. They were on regular chelation with desferrioxamine and oral deferasirox or deferiprone.

Exclusion criteria

- Those children who had a history of respiratory infections or who performed PFT poorly due to technical reasons were excluded.

Blood samples were collected for pre-transfusion Hb (measured by Coulter analyzer) and serum ferritin levels (measured by electrochemiluminescence technique using Cobas 6000 analyzer). Ferritin values are known to correlate with liver iron content directly and hence were assumed to reflect lung iron content also.[8]

Spirometry was performed according to the recommended guidelines by American Thoracic Society (ATS) criteria using COSMED PFT.[9] The child was made to sit comfortably by loosening tight clothing and instructed to take a full breath in and blow out as hard and fast as possible. Care was taken to ensure that inspiration was full and unhurried. A minimum exhalation time of 6 seconds was applied to obtain maximal FVC results, and flow volume loops were generated. The best values of FVC, FEV1 were selected from three technically acceptable maneuvers, and compared with predicted values. The result was expressed as volume in litres at body temperature and pressure, saturated with water vapour (BTPS). The predicted percentage was calculated for the parameters. FVC% and FEV1% <80% were considered to be low. The ratio of FEV1 to FVC was expressed as a percentage and <0.7(70%) was considered low.[9] Grading of the severity of abnormality was done based on the FEV1 % into mild (70-80%), moderate (60-69%) and severe (<60%).[9]

Statistical analysis

SPSS statistical software (version 21) was used for the analysis and values were reported as mean±SD (for values following a normal distribution). The degree of association between all variables studied was analyzed using Pearson coefficient of correlation. The combined effect of several variables on the severity of restriction was analyzed using multiple regression analysis. Summary data are presented using correlation coefficients. Results were considered statistically significant if $p < 0.05$.

RESULTS

Out of 34 subjects, 21 were boys (61.8%) and 13 girls (38.2%). Mean age for the whole group was 14.18±4.95 years. Mean duration of chelation for the whole study group was 7.94±3.78 years. Majority of them were on transfusion since 1st year of life and the mean number of years of transfusion for the group was 13.76±5.01 years. Mean pre-transfusion Hb for the group was 6.7±0.8g/dL, ranging from 4.9-8.1g/dL.

Mean transfusion volume received was 140.93±52.6ml/kg/year ranging from 45.3-231ml/kg/year. Mean S. Ferritin levels of the group observed were 3610.82±2679.51ng/mL ranging from 377-11171ng/mL. S. ferritin levels of the group did not show any significant correlation with age, years of transfusion and years of chelation.

Percentage predicted of FVC and FEV1 was proportionately reduced with the mean values of 67.26±14.01% and 64.00±13.27% respectively. FEV1/FVC of the group in this study was >0.7 (70% of predicted) (mean 98.79%±6.10%) for all subjects indicating a non-obstructive pattern of PFT. Values were almost similar among boys and girls.

Among the 34 thalassemic children subjected to PFT, 73.5% (25 out of 34) were found to have a restrictive pattern (FEV1 <80%) and the remaining 9 were normal. A majority of them had a severe abnormality (14 out of 25) (Table 1).

Table 1: Comparison of severity of restriction (FEV1%) with sex, age and ferritin values in children with restrictive pattern on PFT (n=24).

Restrictive pattern (FEV1%)	Male (n=17)	Female (n=8)	Age in years (mean±SD)	Ferritin (ng/mL) (mean±SD)
Mild (70-80%) (n=4)	1	3	12.74±4.05	2119.95±2038.58
Moderate (60-69%) (n=7)	4	3	14.54±6.04	4601.00±3014.20
Severe (<60%) (n=14)	12	2	16.51±4.72	3587.77±2463.21

There was a statistically significant negative correlation observed between FEV1% and age (r=-0.577, p=<0.01), indicating that severity of restriction increased with increasing age. There was no significant linear correlation between restrictive lung disease and serum ferritin level (r=-0.06, p=0.75). Multiple regression analysis was conducted to see the combined effect of age, years of chelation and ferritin level on FEV1%.

Table 2: Relation between severity of restriction (FEV1%) and age, years of transfusion and chelation, ferritin (n=34).

	Mean±SD	Pearson's correlation coefficient (r value)	p value
Age	14.17±4.95	-0.577	<0.01
Years of transfusion	13.76±5.01	-0.572	<0.01
Years of chelation	7.94±3.78	-0.385	0.02
Ferritin (ng/mL)	3610.82±2679.51	0.06	0.75

Using the enter method, it was observed that age, years of chelation and serum ferritin explain a significant amount of the variance in FEV1% values (F (3,30) =5.86, p<0.05, R2=0.37). However, when individually assessed, the analysis showed that only age significantly predicted the value of FEV1%.

The relation between FEV1% and ferritin adjusted for effect of age and years of chelation can be given by the equation: FEV1 (% predicted) =91.74-1.408 (Age)-0.001 (Ferritin)-0.674 (years of chelation) (with R^2 value=0.370). No significant relationship was found between PFT and serum ferritin levels (p=0.38).

DISCUSSION

Over the last few decades, research has revealed various PFT results in children with thalassemia. Majority of the subjects had a restrictive abnormality (73.5%) which is similar to other studies.[1-4] All the children had FEV1/FVC 0.7, hence ruling out an obstruction. It was almost identical in both boys and girls and was in concurrence with other studies.[2,10] FVC % and FEV1% had a statistically significant negative correlation with age in cases with the restrictive pattern. Few studies[3,4] showed similar results. However, few showed no relation.[2,11]

In the present study, serum ferritin levels of the group did not show significant correlation with age, years of transfusion and years of chelation. However, in a study by Carnelli et al, ferritin was found to have a positive correlation with age (n=62, r=0.29, p=0.02).[1] The present study showed a significant correlation with age indicating that duration of iron overload is more critical in pathogenesis. Factor et al[3] had made a similar observation.

No relation between restrictive pattern and serum ferritin levels was observed in the present study which was in line with other studies.[2,3,11-15] However, a study conducted by Kanj et al showed that PFT (restriction pattern) correlated with serum ferritin.[16] Ferritin may not accurately reflect the total iron burden, and its levels change during the process of chelation.[3,17] Ferritin is an acute phase protein and a product of hepatocellular damage, and it can be elevated in infection, congestive heart failure, and hepatitis.

The reason behind the restrictive pattern is still not clear. In a study by Witzelban et al, necropsy data showed that iron was predominantly found in bronchial glands and epithelial cells rather than in the parenchyma.[18] Tai and colleagues proposed that diffusional impairment caused due to defect in the alveolocapillary membrane could account for the altered lung function as studied in a significant number of subjects with thalassemia.[19] Many other studies reflected that both degree and duration of iron overload may be important and postulated that iron might be responsible for this dysfunction, through a free radical-induced injury.[1,3] An obstructive pattern was observed as the most common type of lung dysfunction in thalassemia in few studies.[5-7]

CONCLUSION

Authors, therefore, consider it important to determine whether there is impaired pulmonary function in patients with β thalassemia major receiving blood transfusions chronically.

Tests of lung function would offer a relatively simple and non-invasive method for following the disease course and the effectiveness of therapy. Good compliance with chelation therapy is crucial to prevent complications in

transfusion-dependent thalassemia patients and that PFTs must be regularly scheduled during the follow-up of these patients.

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