RESEARCH PAPER

Pulmonary Function in Children With Transfusion-Dependent Thalassemia and Its Correlation With Iron Overload

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Objective: To assess the pulmonary function of children with transfusion-dependent thalassemia, and to correlate its pattern with serum iron status. **Methods:** Cross-sectional study done in the pediatrics department of a tertiary care hospital from June, 2018 to May, 2019. 66 children aged 5-18 years with β-thalassemia and HbE/β-thalassemia, admitted for blood transfusion, and with a history of minimum 20 transfusions, were enrolled. Estimation of forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio by spirometer, estimation of serum ferritin and CRP, and chest *X*-rays were done in all the participants. **Results**: 53 (80.3%) children had HbE/β-thalassemia, and 47 (71.2%) showed restrictive pulmonary dysfunction. The mean serum ferritin with impaired pulmonary function was 5616 (70.34) ng/mL and serum ferritin level had significant correlation with pulmonary function (P<0.001). **Conclusion**: Restrictive pattern of pulmonary dysfunction was common in children with thalassemia, and body iron status had a significant association with pulmonary impairment.

Keywords: HbE/β-thalassemia, Serum ferritin, Spirometry.

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Hemoglobin E (HbE)/β-thalassemia, a double heterozygote for HbE and β-thalassemia, is the genotype responsible for approximately one-half of all severe β-thalassemia worldwide [1]. Both in β-thalassemia and HbE/β-thalassemia, repeated transfusions lead to iron deposition in the pulmonary interstitium causing pulmonary hemosiderosis, resulting in slowly worsening pulmonary function [2]. Most studies have reported a restrictive pattern of pulmonary dysfunction [2-10]. Previous studies have shown a positive correlation between iron overload and pulmonary dysfunction, but some others have shown no such association [2-10].

The iron overload associated with chronic transfusions in patients with HbE/β-thalassemia is similar to that observed in patients with β-thalassemia [11], but not much information is available on pulmonary impairment due to iron overload in HbE/β-thalassemia. Studies done from India on this topic is scarce and there is no published data from the eastern part of the country, which has a high prevalence of hemoglobinopathies and thalassemia [12]. The present study was conducted with the objectives of assessing the presence, type and extent of pulmonary impairment in children with transfusion-dependent thalassemia and HbE/β-thalassemia, and to correlate it with the body iron status.

METHODS

This cross-sectional study was done in the pediatrics department of a tertiary care teaching hospital of North East India, from June, 2018 to May, 2019. Ethical clearance was taken from the institutional ethics committee before the start of the study.

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Study subjects were children aged 5-18 year, diagnosed as β-thalassemia and HbE/β-thalassemia (by High performance liquid chromatography), who were on regular blood transfusions i.e., two-to-five weekly since the diagnosis of the disease. Inclusion criterion was children who had received a minimum of 20 blood transfusions. Children who had undergone bone marrow transplantation and those who could not perform spirometry were excluded. Children were enrolled in the study after taking informed consent from the parents, and assent from the children. In our hospital, deferasirox is started at the dose of 20-40 mg/kg in children under regular follow-up, once serum ferritin exceeds 1000 µg/mL; however, it is not provided free of charge at our institution.

After recording detailed history and clinical examination, investigations done were *i*) estimation of

serum ferritin, hemoglobin and C-reactive protein (CRP) level, *ii*) lung function tests and *iii*) chest *X*-ray. CRP was estimated to rule out the possibility of any underlying inflammation or infection which can also cause an increase in serum ferritin level and impairment in pulmonary function.

Outcome measures were serum ferritin level (to assess the body iron status) and lung function tests [forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio] by a desktop spirometer, MIR Spirolab II (Medical International Research). Spirometry was repeated thrice and the best among three values was taken as final. Interpretation of spirometry findings was done by the authors in consultation with a pulmonologist.

A FEV1/FVC ratio <70%, where FEV1 is reduced more than FVC signifies an obstructive defect like chronic obstructive pulmonary disease and asthma [13]. A FEV1/FVC ratio >70% where FVC is reduced more than FEV1, is seen in restrictive defects such as interstitial lung diseases and chest wall deformities [13]. In restrictive disorders; however, FEV1/FVC ratio is normal or high (normal value is above 0.75-0.85, which is age dependent) and the total lung capacity (TLC) is less than 80% of predicted. According to American Thoracic Society [14] grading for the severity of restrictive disorders in the absence of TLC, mild is >70% of predicted value, moderate is 60-69 %, moderately severe is 50-59%, severe is 35-49 % and very severe is <35 % of predicted value.

Statistical analysis: Data were analyzed in MS Excel 2010. Pearson correlation coefficient was used to find out the correlation of pulmonary dysfunction with age, height, serum ferritin level and number of blood transfusions. *P* value < 0.05 was taken as significant.

RESULTS

Out of 76 children identified; 10 children were excluded (9 children could not perform spirometry and 1 underwent bone marrow transplantation) and 66 children (35 males, mean (SD) age 9.55 (2.81) year) were enrolled (**Table I**); 29 (43.9%) of children were diagnosed before the age of two year. The mean number of blood transfusions was 78.5 (43.1), with children in the 9-12 year age group having had maximum blood transfusions [mean (SD) 80.8 (39.6)].

Only ten children were taking oral iron chelators (regularly or irregularly). Mean (SD) serum ferritin level was 3017.65 (2020.88) ng/mL. As expected, the mean (SD) serum ferritin values were lower in children receiving iron chelators as compared to those not receiving iron chela-tors (*n*=56) [743.0 (122.2) vs 3423.8 (1927.5) (*P*<0.001)]. Majority of children with thalassemia had decreased FVC [mean (SD) 74.2% (12.6%)] and normal or comparatively higher FEV1 [mean (SD) 80.8% (12.5%)]. Thus FEV1/FVC was high in all the participants [mean (SD) 1.04 (0.08)], indicating a restrictive pattern of pulmonary dysfunction.

Table I Baseline Characteristics of Children With Thalassemia Enrolled in the Study (*N*=66)

Parameter	*No. (%)*
Age (y)	
5-8	25 (37.9)
9-12	32 (48.5)
13-18	9 (13.6)
HbE/β-thalassemia	53 (80.3)
Stunting	
Moderate	22 (33.3)
Severe	3 (4.5)
Wasting	
Moderate	3 (19.7)
Severe	6 (9.1)
Intake of iron chelator	10 (15.1)

Majority (40.91%) of children had mild restrictive pattern of pulmonary impairment. The mean serum ferritin in children with pulmonary impairment was significantly higher than those with normal pulmonary function (*P*<0.001) (**Table II**). There was a significant negative correlation between serum ferritin level and FVC (r=-0.89; *P*<0.001) (**Fig. 1**). There was a significant correlation of pulmonary function with number of blood transfusions (r=-0.61, *P*<0.001) but not with height (r=0.09, *P*=0.495376) or age (r=0.23, *P*=0.06). Chest *X*-rays were normal in all the participants.

DISCUSSION

This study to assess lung function in 66 transfusion-dependent children (80.3% with HbE/β-thalassemia) with thalassemia found restrictive pulmonary dysfunction in 47

Table II Severity of Pulmonary Impairment and Serum Ferritin Levels in Children With Thalassemia (*N*=66)

Pulmonary impairment	*No. (%)*	*Serum ferritin*
Normal	19 (28.8)	735.83 (118.1)
Mild	27 (40.9)	2719.19 (150.4)
Moderate	15 (22.7)	4943.73 (562.6)
Moderately severe	2 (3.0)	6795.00 (7.1)
Severe	3 (4.5)	8006.67(5.8)

Ferritin values in ng/mL. P<0.001.

WHAT THIS STUDY ADDS?

- Iron overload is associated with restrictive type of pulmonary impairment in children with β-thalassemia and HbE/β-thalassemia.

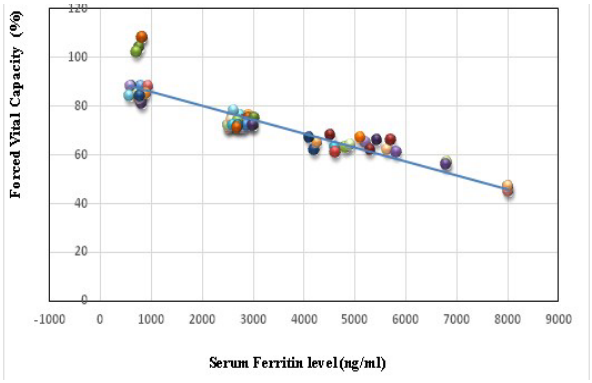

Fig. 1 Scatter plot depicting a negative correlation between serum ferritin level and forced vital capacity (r=-0.89; P<0.001).

(71.2%) children. Serum ferritin level had significant correlation with pulmonary function.

The proportion with HbE/β-thalassemia in this study was similar to a previous study from Assam [12]. In most studies done on pulmonary function in patients of thalassemia, majority of study participants were β-thalassemia major. Despite having a large number of Hb E-β thalassemia cases in this study, the pattern of pulmonary dysfunction did not significantly differ from previous studies [2-10] where most patients were β-thalassemia major, as Hb E-β thalassemia behaves similar to β-thalassemia, both phenotypically and in iron overloading pattern. [11]. Three Indian studies found serum ferritin levels similar to us among children with thalassemia [4,6,10], though a few others reported lower levels ranging from 1180-1594 ng/mL [3,5,7].

Previous studies have shown restrictive type of lung impairment in the range of 35-95% [2-10]. Two pediatric studies reported mild degree of impairment in 23.8% [3] and 42% [7] of children, similar to our study (40.9%). But another study reported severe restrictive type in 14 (73.5%) children [10]. Correlation between pulmonary dysfunction and iron overload was stated by some authors [2-5]. According to one study, fibrosis and interstitial edema, which are due to iron overload, cause lung dysfunction [3]. We found a significant negative correlation between serum ferritin level and pulmonary impairment. On the other hand, few have found no association between iron overload and severity of pulmonary dysfunction [6]. We found significant correlation with number of blood transfusions but not with age, similar to a previous report [2]. However, a few studies have reported correlation with age, height and duration of chelation [6,10].

Our study had the limitations of non-availability of TLC measurement, small numbers, and only 15.1% children receiving chelation therapy.

In conclusion, we have found restrictive pattern of pulmonary dysfunction of varying severity in children with thalassemia, including HbE/β-thalassemia, with significant association between severity of pulmonary impairment and body iron stores. Pulmonary function tests should be done regularly like other organ function monitoring as deranged lung function shows very few or no symptoms.

Ethics clearance: Institutional Ethics Committee, Assam Medical College; No. ECR/636/Inst/AS/2014 dated Sep 24, 2019.
Contributors: AB: conceptualized the study, analyzed data, reviewed literature, revised the manuscript and critically reviewed; JB: conceptualized the study, collected data, searched literature, analyzed data, drafted the manuscript. Both the authors approved the final manuscript, and are accountable for all aspects related to the study.
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