Section: Pediatrics

Original Research Article

PULMONARY DYSFUNCTION IN TRANSFUSION DEPENDENT THALASSEMIA PATIENTS

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Abstract

Background: Thalassemia major is a severe form of thalassemia, a genetic blood disorder characterized by the body's inability to produce hemoglobin properly. Children with thalassemia major typically require regular blood transfusions to manage their condition and maintain adequate hemoglobin levels. While blood transfusions are essential for managing thalassemia major, the risk of iron overload is a significant concern that requires careful management to prevent long-term complication. **Materials and Methods:** This cross-sectional analytical study involved 54 children diagnosed with transfusion-dependent thalassemia. The study conducted pulmonary function tests (PFTs) and assessed iron levels (serum ferritin) in these children. PFTs included spirometry, and the study aimed to establish correlations between pulmonary function and iron load.2D -ECHO was done to exclude any cardiac dysfunction. **Result:** Among the participants who underwent pulmonary function tests (PFTs), 38.89% were identified with restrictive dysfunction, 12.96% with obstructive dysfunction, and 29.63% with mixed dysfunction. Within the restrictive dysfunction subgroup, 42.9% showed mild dysfunction, 19% had moderate dysfunction, and 38.1% exhibited severe dysfunction. In participants with serum ferritin levels exceeding 2000 ng/ml, 75% displayed severe restrictive dysfunction, while 25% demonstrated moderate dysfunction, with no cases of mild dysfunction observed($p<0.016$). **Conclusion:** Among chronically transfused beta thalassemia children, restrictive pulmonary dysfunction predominated, the severity of which correlated significantly with higher serum ferritin levels, indicating a role of iron in its pathogenesis.

INTRODUCTION

Pulmonary dysfunction is increasingly recognized as a prevalent issue among individuals with transfusion-dependent thalassemia (TDT).[1-5] The mechanisms contributing to lung injury in TDT include complications associated with regular blood transfusions, chronic hypoxia, pulmonary hemosiderosis, pulmonary hypertension, and concurrent cardiac dysfunction. Restrictive lung injury has been documented as a frequent pattern of pulmonary dysfunction in TDT in several previous studies.[1,2] However, other patterns such as obstructive and mixed pattern have also been reported.[4,5]

In patients with thalassemia major (TM), higher serum ferritin levels were observed in those with impaired pulmonary function compared to those with normal pulmonary function in previous studies.[6]

The rationale for conducting this study stems from the observation that pulmonary dysfunction persists in transfusion-dependent thalassemia patients despite undergoing chelation therapy

Objectives

1. To study the pulmonary dysfunction in transfusion dependent thalassemia patients.
2. To categorize the pulmonary dysfunction into obstructive or restrictive lung disease in transfusion dependent thalassemia patients.
3. To find out the correlation between iron overload and pulmonary dysfunction in transfusion dependent thalassemia patients.

MATERIALS AND METHODS

Study Design & Setting: The present analytical study was conducted in the Department of Pediatrics of a tertiary care hospital in central India, spanning from July 2022 to June 2024. Ethical clearance was obtained from the Institutional Ethical Committee prior to commencing the study.

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Inclusion Criteria

The study included children aged 6-14 years diagnosed with β-thalassemia via High Performance Liquid Chromatography, who received regular blood transfusions (two-to-five weekly) since diagnosis and have received over 200 ml/kg of blood transfusions in the past two years after obtaining informed consent from parents and assent from the children.

Exclusion criteria

Transfusion dependent thalassemia patients with acute respiratory infections, pulmonary tuberculosis, congestive cardiac failure, inability to perform spirometry, chest wall disorders, and echocardiographic evidence of systolic dysfunction, diastolic dysfunction grade 4, or pulmonary hypertension.

Methods: All Children enrolled in study were started with deferasirox at a dose of 20-40 mg/kg for children under regular follow-up once serum ferritin levels exceed 1000 ng/mL.

Following comprehensive history-taking and clinical examination, the investigations conducted included:

Measurement of serum ferritin, hemoglobin, and C-reactive protein (CRP) levels,

Lung function tests- Forced expiratory volume in one second (FEV1), Forced vital capacity (FVC), and the FEV1/FVC ratio—performed using a desktop spirometer, RMS HELIOS version 3.1.85. Spirometry was conducted three times, and the best result from these trials was selected as the final measurement. Interpretation of spirometry results followed the standards set by the American Thoracic Society (ATS) and the European Respiratory Society (ERS).

Chest X-ray. CRP levels were assessed to exclude underlying inflammation or infection, which can potentially elevate serum ferritin levels and impact pulmonary function.

In obstructive defects such as chronic obstructive pulmonary disease (COPD) and asthma, a FEV1/FVC ratio below 80% indicates that FEV1 is reduced more than FVC. Conversely, in restrictive disorders, the FEV1/FVC ratio remains normal or high, while FVC is less than 80% of the predicted value. According to the American Thoracic Society's grading system for the severity of restrictive disorders, mild severity corresponds to FVC less than 80% of the predicted value, moderate severity to less than 60%, and severe severity to less than 50% of the predicted value, in the absence of total lung capacity (TLC) data.

Statistical analysis was conducted using MS Excel 2019. The Pearson correlation coefficient was employed to assess the relationship between pulmonary dysfunction and serum ferritin levels. A significance level of $P < 0.05$ was considered statistically significant.

RESULTS

Fifty-four children were included in study. Out of 54, 36 were males and 18 were females. The mean age of study population was 8.91 ± 2.37 years.

All participants were receiving oral iron chelators, either regularly or irregularly. The mean serum ferritin level was 1646 ± 627.96 ng/ml, and it was lower in children receiving iron chelators regularly compared to those receiving them irregularly.

A majority of children exhibited reduced forced vital capacity (FVC) and normal or increased forced expiratory volume in one second (FEV1), resulting in a high FEV1/FVC ratio suggestive of a restrictive pattern of pulmonary dysfunction observed in 38.89% of the total participants.

Among those affected, 42.9% showed a mild restrictive pattern of pulmonary impairment. Children with pulmonary impairment had significantly higher mean serum ferritin levels compared to those with normal pulmonary function. A notable negative correlation was found between serum ferritin levels and FVC ($r = -0.89$; $P < 0.001$). Additionally, there was a significant correlation between pulmonary function and the number of blood transfusions ($r = -0.827$, $P < 0.01$). Chest X-rays showed normal findings in all participants.

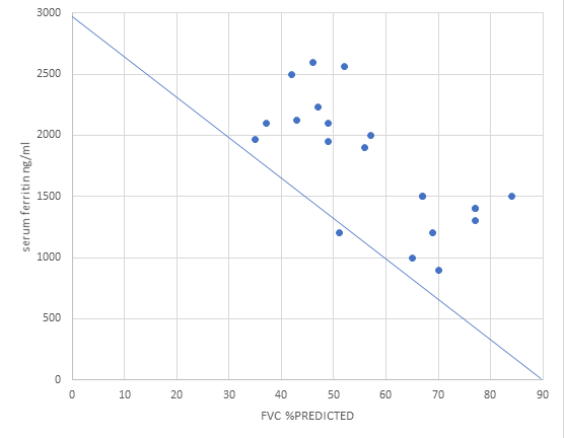

Table 1: FEV1/FVC interpretation among Study Population (n-54).

FEV1/FVC interpretation	Number (n)	Percent (%)
Restrictive	21	38.89
Obstructive	7	12.96
Mixed	16	29.63
Normal	10	18.52
Total	54	100

Table 2: Grading of restrictive dysfunction among Study Population (n=21)

Grading of Restriction	Number (n)	Percent
Mild Restrictive	9	42.9%

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Moderate Restrictive	4	19.0%
Severe Restrictive	8	38.1%
Total	21	100%

Table 3: Association between Serum Ferritin and Restrictive dysfunction severity among Study Population.

S. ferritin	Restrictive dysfunction severity			Total	P value
	Mild	Moderate	Severe		
<1000 ng/ml	2	0	0	2	0.016
	22.2%	0.0%	0.0%	9.5%	
1000-2000 ng/ml	7	3	2	12	
	77.8%	75.0%	25.0%	57.1%	
>2000 ng/ml	0	1	6	7	
	0.0%	25.0%	75.0%	33.3%	
Total	9	4	8	21	
	100.0%	100.0%	100.0%	100.0%	

DISCUSSION

This study aimed to evaluate type of pulmonary dysfunction in Transfusion Dependent Thalassemia (TDT) patients, focusing on obstructive or restrictive lung disease and their correlation with iron overload. Analysis of FEV1/FVC% among participants revealed varied patterns:

- 18.52% had a normal ratio.
- 12.96% showed obstructive dysfunction.
- 29.63% exhibited a mixed dysfunction pattern.
- 38.89% demonstrated restrictive dysfunction.

Among those with restrictive dysfunction:

- 42.9% had mild impairment.
- 19% had moderate impairment.
- 38.1% had severe impairment.

In the present study, the higher prevalence of restrictive lung patterns can be attributed to factors such as non-compliance with chelation therapy, lack of parental awareness, limited availability of chelation treatment, and inadequate dosing of chelation agents. Despite receiving chelation therapy, iron overload persisted at levels sufficient to cause restrictive dysfunction in our subjects.

In contrast to prior studies,[5] the present study revealed a higher prevalence of obstructive dysfunction (12.96%), potentially influenced by comorbidities such as asthma or hyperactive airway disease among our study cohort. Additionally, 37% of participants did not adhere to chelation therapy due to parental unawareness and logistical challenges in accessing distant treatment centers from their residences. Unlike studies using DLCO,[1] our assessment relied on FVC due to equipment limitations, impacting the severity grading of restrictive dysfunction.

Similar to Guidotti et al. (2017),[2] this study observed a predominance of restrictive patterns. Mean serum ferritin levels were 1646.17 ± 627.96 ng/dl, with 51.85% falling between 1000-2000 ng/ml, 27.78% between 2001-3000 ng/ml, and 20.37% below 1000 ng/ml. Notably, higher serum ferritin levels correlated with more severe restrictive dysfunction in our study, particularly among those with levels exceeding 2000 ng/ml, where 75% exhibited severe restrictive dysfunction. These findings highlight the crucial role of iron chelation therapy in managing iron overload-related complications, including restrictive lung disease, in individuals with transfusion-dependent thalassemia.

These findings highlight the imperative role of managing iron burden effectively through chelation therapy to prevent or mitigate restrictive lung disease in individuals with transfusion-dependent thalassemia.

In the present study, an increase in blood transfusion volume correlated with a predominantly restrictive pattern of pulmonary dysfunction among subjects. Additionally, higher blood transfusion volumes were associated with increased severity of restrictive dysfunction.

Kate C. Chan et al,[7] (n=101) found that in transfusion-dependent thalassemia patients, chronic exposure to multiple packed red blood cell transfusions leads to systemic iron overload, compounded by insufficient iron excretion. Iron accumulation contributes to lung parenchymal fibrosis, architectural distortion, and oxidative stress, promoting a restrictive lung disease pattern.

In contrast, F. Rahim et al,[8] (2008) (n=59) reported that chest X-ray findings did not consistently reflect the severity of pulmonary dysfunction; some patients with severe restriction had normal chest X-rays. Their study did not identify a linear relationship between serum ferritin levels and the extent of restriction.

These findings emphasize that serum ferritin levels alone may not fully assess total iron overload or predict pulmonary dysfunction outcomes in thalassemia patients. Furthermore, our study and others consistently observed normal cardiac function, with all patients exhibiting an ejection fraction > 60%, indicating consistent cardiac health across different investigations.

What this Study ADDS?

Restrictive dysfunction correlates with iron overload in transfusion dependent thalassemia patients.

Regular monitoring of PFT through spirometry shall be included in the follow up of these patients as a cost effective tool.

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CONCLUSION

In summary, pulmonary dysfunction manifests in asymptomatic transfusion-dependent thalassemia patients regardless of cardiac function. Various patterns including restrictive, obstructive, and mixed types are observed. Restrictive pulmonary dysfunction predominates among chronically transfused beta thalassemia children, with severity correlating significantly with higher serum ferritin levels, implicating iron in its pathogenesis.

Mechanisms of lung injury encompass pulmonary hemosiderosis, pulmonary hypertension, free radical-induced parenchymal damage, and parenchymal fibrosis due to iron accumulation. Regular pulmonary function testing, incorporating spirometry, plethysmography, and DLCO assessment, is recommended for early dysfunction detection.

Assessing serum ferritin every six months as an indicator of iron overload is crucial for optimizing chelation therapy. Parental education on the complications of regular transfusions and adherence to chelation therapy are essential to mitigate iron overload and its complications in thalassemic patients.

Although spirometry is a cost-effective and easily accessible method for evaluating pulmonary dysfunction, it does not provide comprehensive assessment of conditions such as diffusion defects, total lung capacity, and residual lung volume. Nonetheless, spirometry remains a valuable tool suitable for use in resource-constrained settings.

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