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Evaluation of Pulmonary Dysfunctions in Iron Overloaded Beta Thalassaemia Children: A Study at Teaching Hospital of Rahim Yar Khan, Pakistan

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Author`s Contribution

All authors contributed significantly to this work, participating in conception, study design, data acquisition, analysis, and interpretation. They were involved in drafting, revising, and critically reviewing the article, ultimately giving their approval for the version to be published

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ABSTRACT

Objectives: To evaluate the pattern of pulmonary dysfunction in iron overloaded beta thalassemia children and its correlation with serum ferritin.

Methodology: This cross-sectional study was conducted from April 2024 to September 2024 in Pathology Department and Department of Pulmonology at Sheikh Zayed Medical College/Hospital, Rahim Yar Khan. Transfusion dependent thalassaemia children bearing more than 10 years of age, ferritin levels greater than 1000ng/ml and bearing record of more than 20 transfusions were included in the study. Standardized pulmonary function test was conducted with spirometry. Serum ferritin levels were used to measure iron overload.

Results: A total of 115 individuals were examined; 47 percent were female, and 53 percent were male. Spirometry revealed respiratory impairment in 10.43% of patients with obstructive pattern and 31.30% with restrictive pattern. The average ferritin level observed was 3167.5 ng/ml. Of these, 2.6% were highly obstructive, 4.3% moderately restricted, 5.7% mildly restrictive, and 11.3% were very restrictive. 58.3% of the total had normal values. The degree of pulmonary impairment and ferritin levels did not appear to be related.

Conclusion: In children with iron over loaded transfusion dependent thalassaemia disease, restrictive pattern is the most common pulmonary dysfunction. Patients with abnormal PFTs ought to have their compliance with the transfusion program and re-evaluation of chelation therapy. It is necessary to use spirometry to screen all children for thalassaemia for early diagnosis of respiratory impairment.

Keywords: Thalassaemia, Pulmonary Dysfunction, Iron overload, multi-transfused thalassaemia.

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Introduction

Thalassaemia is the most common type of recessively inherited disease in the world, characterized by decreased or no hemoglobin production and a chronic anemia of varying degrees of severity. Hemoglobin is essential for the binding and transport of oxygen and carbon dioxide by red blood cells, and it also affects the shape, stability, and half-life of these cells. The specific kind of mutation that causes thalassaemia results in decreased production of structurally normal globin chains.[1] Clinically, there are two basic forms of thalassaemia based on whether the patient requires blood transfusions. Patients with transfusion-dependent thalassaemia who experience severe anemia in their early years and need constant blood transfusions for the rest of their lives to survive.

Conversely, patients with non-transfusion-dependent thalassaemia who typically experience mild to moderate anemia in later childhood or even adulthood, and under specific clinical circumstances, they may only need sporadic or brief-term regular transfusions.[2] This recessively inherited disease, β-thalassaemia, is a hereditary hemoglobin ailment caused by a deficiency in the β-globin chain of hemoglobin. The homozygous or compound heterozygous versions indicate that there is an imbalance in the formation of the α- and β-chains, leading to inefficient and reduced red blood cell production.[3] Two of the most common signs and symptoms of beta thalassaemia that are usually observed between the ages of 6 and 24 months are jaundice and hypochromic microcytic anemia. Hemoglobin levels >7 are common in persons with intermediate thalassaemia, nevertheless.[4]

Since thalassaemia is a genetic disorder that can be passed from parents to children, consanguineous marriage is one of the major influencing factors for the disease. There is a 25% chance that a child with thalassaemia major will be born during each pregnancy when both parents are carriers. There is a 50% probability that a child with thalassaemia major will be born during each pregnancy if one carrier marries a major patient. Therefore, in order to prevent this autosomal recessive syndrome, it is recommended to avoid consanguineous marriage.[5]

Transfusion-dependent thalassaemia is most common in the Mediterranean region, which includes countries close to the north coast of Africa, South America, Southern China, the Middle East, Central Asia, and the Middle East. According to the World Health Organization (WHO), thalassaemia is a chronic illness that seriously shortens the lives of affected individuals in 60 different nations. Over 50% of the 70,000 newborns with thalassaemia major each year also have thalassaemia minor. In Iran, there are around 3 million thalassaemia carriers and 26,000 individuals with thalassaemia major. The World Health Organization (WHO) reports that thalassaemia, which affects 280 million individuals globally, claimed 16,800 lives.[6] Transfusion dependent thalassaemia is one of the most common inherited hemoglobin diseases in Pakistan with a gene carrier rate of 5-7% and an estimated 9.8 million carriers in the general population. In Pakistan, the average age is still about ten years old. This discrepancy can be attributed to the lack of adequate, well-maintained transfusion facilities, which raises the risk of iron overload, hepatotoxicity, transfusion-associated infections, and cardiac issues. The most severe kind of beta-thalassaemia requires iron chelation therapy and continuous transfusions for life.[7] The other reported complication of iron overload are cellular dysfunction, apoptosis, fibrosis, and necrosis in target organs, including the myocardium, liver, lungs and endocrine glands.[8]

Serum ferritin levels in healthy individuals typically vary from 12 to 300 μg/L for men and 12 to 150 μg/L for women. Serum ferritin levels > 1000 μg/L are indicative of iron overload and have been associated with adverse effects on organ damage, mortality, increased risk of heart disease, liver problems, and lung troubles.[9]

Up to 80% of patients with transfusion-dependent thalassaemia have been reported to have pulmonary dysfunction. Reduced carbon dioxide pattern diffusion capacity and restrictive and obstructive lung diseases are among the pulmonary abnormalities reported in earlier studies.[10] Chronic lung inflammation is a symptom of obstructive pulmonary disorders, which can lead to respiratory compromise and discomfort in the end. Breathlessness, copious sputum production, and a persistent cough are the disease's defining symptoms. The patient's quality of life is severely reduced, and their respiratory function gradually deteriorates. Restrictive lung disease is a severe lung pathology distinguished by decreased lung volumes, as opposed to COPD. Reduced lung volumes can result from extrinsic factors like diseases of the pleura, chest wall, or neuromuscular apparatus, or from intrinsic factors like changes in the lung parenchyma. They most frequently result from lung interstitial disease that follows fibrosis. There is a decrease in expiratory airflow relative to lung volume.[11] Changes in pulmonary function have been linked to iron overload, and patients with transfusion-dependent thalassaemia generally have abnormal pulmonary function tests (PFTs). Pulmonary dysfunction has numerous, intricate pathophysiological reasons.[12]

Most surveys revealed a predominantly restricted tendency on spirometry. However, a number of investigations revealed that an obstructive pattern was predominant.[13] Patients with transfusion-dependent thalassaemia also exhibited iron-loaded macrophages, suggestive of unexplained pulmonary hemosiderosis, and copious sideroblasts in lung lavage and alveolar gaps. These findings are diagnostic of alveolitis. By generating potentially dangerous hydroxyl radicals, iron accumulation can lead to lung parenchymal fibrosis and impairments in restrictive lung function.[10] Reduced carbon monoxide diffusing capacity has been associated with both of these patterns.[14]

Our goals in this study were to determine the patterns of pulmonary function deficits in patients with transfusion-dependent thalassaemia and to investigate the relationships between abnormalities in pulmonary dysfunction and serum ferritin level.[10]

Table III: PFT's Findings with Percentage within Ferritin Level

Ferritin (ng/ml)	Normal (% within ferritin)	Mild (% within ferritin)	Moderate (% within ferritin)	Severe (% within ferritin)	Total (% within ferritin)
<2500	28(62.2%)	11(24.4%)	3(6.7%)	3(6.7%)	45(100%)
2500-4000	27(61.4%)	10(22.7%)	2(4.5%)	5(11.4%)	44(100%)
>4000	12(46.2%)	6(23.1%)	3(11.5%)	5(19.2%)	26(100%)

Methodology

This cross-sectional study was carried out at the Departments of Pathology and Pulmonology of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, from April 2024 to September 2024 with approval from the Institutional Review Board (IRB). After giving their informed consent, children with transfusion-dependent thalassaemia who were more than ten years old, with ferritin levels above 1000ng/ml, and receiving more than 20 blood transfusions were included in the study. Their blood samples were drawn into vacutainer having clot activator and processed on Cobas E411 to check serum ferritin level by electrochemiluminescence immunoassay method.

Pulmonary function assessment was performed in the pulmonology department on spirometer MIR *A23-0. Y00000* SPIRO BANK II (MIR, Roma, Italy). A sample size of 89 was calculated by Rao Software by taking the expected prevalence of thalassaemia as 8%, 95% of confidence interval and 5 % of margin of error. This calculated sample size of 89 was adjusted to 115 for better precision. Convenient sampling technique was adopted. Patients without discrimination of age and gender were included in this research.

Clinical profile including included detailed history, clinical examination, transfusion history and pulmonary function profiles were part of study. Venous samples were collected from all participants and serum ferritin levels were assessed.

After chest X-ray spirometry was done. Based on spirometry measurements the respiratory impairment pattern (obstructive or restrictive) was described and correlated with serum ferritin. Pulmonary deficits were classified as "mild" (>70%), "moderate" (<70% and >60%), "moderately severe" (<60% and >50%), and "severe" (<50%). Using SPSS version 23, the data was analyzed. Mean and standard deviation were used to present the quantitative data. Frequencies and percentages were used to present the qualitative data.

Results

Out of 115 patients, 54 (47%) were female and 61 (53%) were male. The age distribution of the patients revealed that 2 (1.73%) are older than 20 years, 18 (15.65%) are between 15 and 20 years, and 95 (82.6%) are less than 15 years old. The standard deviation was 3.41 and the mean number of transfusions was 23.5. The distribution of ethnic groups revealed that 82(71.3%) were Saraiki, followed by 30(26.1%) Punjabi, 2(1.7%) Sindhis, and 1(0.9%) Balochi. In Rahim Yar Khan, a district in southern Punjab, Pakistan, the distribution of patients by area revealed that 47 (40.9%) were from rural areas and 68 (59.1%) were from urban areas. As for as number of transfusions was concerned males were frequently transfused (61%) as compared to females (54%). Level of ferritin showed that <2500 ng/ml ferritin level in 45(39.1%) patients while 2500-4000 ng/ml in 44(38.3) patients and >4000 ng/ml in 26(22.6%) patients. PFT findings were normal in 67 (58.3%) subjects, while 48 (41.7%) had abnormalities, including restrictive disease in 36 (31.3%) and obstructive disease in 12 (10.4%), with severity details provided in Table I. Patients with abnormal PFT and ferritin levels <2500 ng/ml had mild (24.4%), moderate (6.7%), and severe (6.7%) pulmonary disease. For ferritin levels of 2500-4000 ng/ml, 22.7% were mild, 4.5% moderate, and 11.4% severe. In those with >4000 ng/ml ferritin, 23.1% were mild, 11.5% moderate, and 19.2% severe (Table II).

Table I: Pulmonary Function Test Findings According to Severity.

PFT Findings	N (%)
Normal	67(58.3%)
Mild Obstructive	9(7.8%)
Mild Restrictive	18(15.7%)
Moderate Obstructive	3(2.6%)
Moderate Restrictive	5(4.3%)
Severe Restrictive	13(11.3%)

Discussion

In the current study, there are 54 (47%) females, and 61 (53%) males. Comparable results from a different study by KC Chan et al. (2023) revealed that there were more men than women, with 51% of the sample.[10] Another study conducted in India showed similar findings with male

dominancy (66%).[15] According to the age distribution, there were 95 patients (82.6%) under the age of 15 years, 18 patients (15.7%) between the ages of 15-20 years, and 2 patients (1.7%), over the age of 20 years. Similar results from a different study carried out in Mangalore indicated that problems cause the mortality of thalassemic patients between the ages of 11 and 14 years.[16] In the current study, the average number of transfusions received by males was 23.07, whereas the average number for females was 24.04, for a total of 23.52 transfusions. Comparable results were also reported in a different study discussed above by KC Chan et al. (2023), with a mean of 23.3.[10]

According to present study, 39.1% of patients had ferritin levels less than 2500 ng/ml, 38.3% had levels between 2000 and 4000 ng/ml, and 22.6% had greater than 400 ng/ml. Ferritin had a mean of 3167.51 ng/ml. Very similar to these findings, a study carried out at Assam Medical College and Hospital (2022) revealing the mean ferritin level of 3017.65ng/ml.[17]

Current study discovered that greater number of patients had normal findings. 67(58.3%) patients have normal and 48(41.5%) have abnormal PFT's findings. Similar results were reported by study conducted in Qazvin University of Medical Science Iran with 60.5% patients having normal PFT's.[14] Similarly another study conducted in Saglik Bilimleri university Adana, Turkey (2019) also shown 57.5% of patients have normal PFT's and 42.5% of patients have abnormal PFT's.[18]

Current study revealed 31.3% restrictive lung disease followed by 10.3% obstructive lung disease. Another study conducted in India showed the similar findings with 32% restrictive lung disease and 10% obstructive lung disease.[15] Similar results were reported by KC Chan et al with 38% restrictive lung disease and 5% obstructive lung disease.[10] The results of our study showed that 15.7% of lung disorders were mildly restrictive, followed by 11.3% severe restrictive, 7.8% mildly obstructive, 4.3% moderately restrictive, and 2.6% moderately obstructive. Similar findings from a different study at Qazvin University of Medical Science in Iran in 2020 indicated that 15.5% of lung disorders were mildly restrictive, 6.06% were mildly obstructive, 6.06% were moderately restrictive, and 6.06% were moderately obstructive.[14]

The current investigation found no evidence of a significant relationship between serum ferritin and the severity of pulmonary abnormalities. In comparison, a study in 2019, carried out in Turkey showed no connection between blood ferritin levels and the severity of pulmonary dysfunction.[18] The study conducted in University Kebangsaan Malaysia, Kuala Lumpur, Malaysia also found no correlation between severity of lung dysfunctions and serum ferritin.[19] Similarly studies carried out at Shiraz University of Medical Sciences in Iran, Research Center Thalassaemia Clinic, Iranian Blood Transfusion Organization Tehran, Iran (2008) and Jordan University of Science and Technology, Jordan (2007) found no association between the pulmonary dysfunction and serum ferritin level (2011).[20,24,21]

Conclusion

This study concluded that the dominant pulmonary disorder in studied population is restrictive respiratory dysfunction under regular transfusion program. Obstructive lung disease is also seen in these patients. Regular monitoring is required, even for asymptomatic thalassaemia patients and it is crucial to improve the quality of life for these poor children. This can be accomplished by using regular pulmonary function tests to assess the respiratory system so that the pulmonary disorders can be addressed timely.

LIMITATIONS: The use of iron chelation therapy in patients who may have lung impairment, small sample size, lack of financing, and impossibility of assessing hepatic iron level by liver biopsy as the optimal quantitative measurement of iron overload were all factors excluded from this study due to the limited resources.

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