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Prevalence of Pulmonary Hypertension in Patients with Thalassemia Intermedia in 2009: a single center's experience

Hassan Mottaghi Moghaddam[1], Zahra Badiei[2], Kambiz Eftekhari[3], Reza Shakeri[4], Hamid Farhangi[5]

[1] Associate Professor of Pediatric Cardiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Associate Professor of Pediatric Hematology & Oncology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Assistant Professor of Pediatric Gastroenterology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran
[4] Fellow of Pediatric Cardiology, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] Assistant Professor of Pediatric Hematology & Oncology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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Abstract

Background: There are various clinical symptoms of thalassemia intermedia, and they lie roughly between those of major and minor forms of the disease. Patients with thalassemia intermedia occasionally require blood transfusions. This renders them susceptible to pulmonary arterial hypertension (PAH) syndrome, which is one of the most significant complications in patients with thalassemia intermedia. PAH is more common in in thalassemia intermedia than in thalassemia major, and it may cause cardiac complications in patients who are older than 30. The objective of this study was to estimate the prevalence of PAH in thalassemia intermedia patients so that they can be referred expeditiously for treatment, thereby preventing the complications that occur later.

Methods: This cross sectional study was conducted under the supervision of hematology department of Mashhad Medical University. Forty-one patients with thalassemia intermedia were examined at the Sarvar Thalassemia and Hemophilia Clinic of Mashhad. Electrocardiography, chest radiography, and echocardiography tests were performed for all of the patients by the same pediatric cardiologist. The data were processed by SPSS software, version 11.5, and the results were analyzed using chi-squared, Student's t, and Mann-Whitney tests.

Results: The mean age of the patients was 21.93±8.34. They had been under pediatric heart specialists' constant examination and treatment since their childhood when they were diagnosed with TI, and continue to receive regular follow-up care. The prevalence of pulmonary hypertension was 24% in our study population. In patients with thalassemia intermedia, the left ventricular (LV) mass indices were about 3-5 times higher than would be expected in a normal population. Patients with higher LV mass indices have a greater risk of developing pulmonary hypertension, and those with serum ferritin levels below 1000 ng/ml are less susceptible to diastolic dysfunction.

Conclusion: Pulmonary hypertension is common in patients with thalassemia intermedia. Irregular chelation therapy or absence of this treatment might lead to diastolic dysfunction, and serum ferritin levels below 1000 ng/ml could be an important factor in preventing the development of diastolic dysfunction or slowing down its progression.

Keywords: thalassemia intermedia, pulmonary hypertension, echocardiography, ferritin

Corresponding author:
Dr. Hamid Farhangi, Dr. Sheikh Pediatric Hospital, Mashad, Iran.
Tel/Fax: +98.5137273943, Email: farhangih@mums.ac.ir
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1. Introduction

The condition, thalassemia intermedia (TI), is milder than major thalassemia, and the symptoms may not appear until early childhood. Patients with this condition do not often require regular blood transfusions. They may have mild anemia with hemoglobin levels ranging between 7 to 10 gr/dl, which may necessitate blood transfusions occasionally. TI patients have a tendency to develop significant complications, which have received less than their due attention. TI patients can have multiple cardiac complications, including pulmonary artery hypertension (PAH) and congestive heart failure. PAH is prevalent in TI patients (1), and heart failure is the most common cause of mortality in patients who have thalassemia major or thalassemia intermedia (2). Heart disease is caused by high cardiac output due to chronic hypoxia of the tissues and vascular involvement, which increases the resistance to blood flow in the pulmonary vessels (3). In certain situations, such as infection, hypersplenism, and some other diseases, TI patients must have blood transfusions. If they fail to maintain hemoglobin levels above 6 gr/dl, they may require regular blood transfusions, splenectomy (especially in cases with hypersplenism) (4), or erythropoiesis inducers, such as hydroxyurea, which are about 75% effective (5). The status of total iron in the body should be carefully monitored, and patients with iron overload should be treated with an intensive iron chelation regimen as soon as possible. Pulmonary hypertension is a major cause of mortality and morbidity in patients with chronic hemolytic anemia. The incidence rate of symptomatic and asymptomatic forms have been reported to be 10% and 5-60%, respectively (6).

Asymptomatic pulmonary hypertension is a leading factor of heart failure and death in thalassemia. Pulmonary hypertension is defined by a mean pulmonary artery pressure of 25 mmHg or higher at rest and 30 mmHg or higher during exercise (7). The exact cause of this condition is unknown. However, anemia and iron overload (even without blood transfusion) have been proposed as the two main risk factors. Other risk factors include chronic hypoxia, long-term effects of splenectomy, coagulation disorders, oxidative stress, and chronic hemolysis (1). Thus, regular blood transfusion and appropriate chelation therapy soon after pulmonary hypertension diagnosis can prevent this advanced complication of the disease (1). Evidently, splenectomy can lead to pulmonary hypertension in patients with thalassemia. There is a high prevalence of pulmonary hypertension in patients with thalassemia intermedia who have not received blood transfusions. Clinical manifestations of pulmonary hypertension include heart murmur, exertional dyspnea, fatigue, lethargy, exertional syncope, chest pain, daytime sleepiness, morning headaches, right ventricular failure, and, eventually, cor pulmonale (7). Echocardiography can show right ventricular hypertrophy and right atrial enlargement (7). Doppler echocardiography is the most reliable, non-invasive method for estimating the pressure in the pulmonary artery and its long-term follow up (7). Right heart catheterization is the standard method that is used in diagnosing pulmonary hypertension (7).Treating pulmonary hypertension primarily is based on treating the underlying disease. The benefits of the use of oxygen in reducing mortality in these patients have been proven. Pharmacotherapy includes calcium channel blockers, sildenafil, Bosentan (endothelin receptor antagonist), prostacyclin (epoprostenol), digoxin, and anticoagulants. Some cases may eventually require surgical intervention (7).

To the best of our knowledge, large, epidemiological studies of PAH have not been performed in Mashhad even though it is an important issue in pediatrics. Thus this study was conducted considering that Mashhad is the referral point of pediatric hematology-oncology in northeast and east Iran. The aim of this study was to determine the prevalence of PAH in thalassemia intermedia patients so they can be referred in time for treatment to prevent later complications.

2. Material and Methods

This was a cross-sectional study in which all thalassemia intermedia patients referred to the Sarvar Clinic in Mashhad in 2009 were observed. (This study was conducted as residency thesis No. 2346). Sarvar Clinic was selected for gathering the data because it is the referral site for hemoglobinopathy and coagulopathy disorders in northeast Iran. Patients were selected using a non-probable (non-randomized) sampling method. This study was approved by Ethics Committee of Mashhad University of Medical Sciences, and it was in compliance with the Helsinki Declaration. Informed consent forms were signed and submitted by all of the participants.

According to the 60% incidence rate of pulmonary hypertension in patients with thalassemia intermedia, the sample size was calculated to be 60 cases (with a relative accuracy of 25%). However, because there was a total of 41 patients referred to the Sarvar Clinic with thalassemia intermedia all of them were enrolled in the study. In the beginning, a questionnaire was completed for each patient. It included demographic information, their mean serum ferritin and hemoglobin levels in the last year, and blood transfusion and chelation therapy (according to their

medical records). Electrocardiograms (ECGs), chest radiographs (CXRs), and echocardiography tests were performed for all patients by the same pediatric cardiologist, and the patients were screened in terms of the blood pressure in their pulmonary arteries. ECG machine was calibrated at 1 mv/10 mm and a chart speed of 25 mm/s. Patients' ECG indexes were analyzed, and the prevalence of each index was calculated in TI patients with and without pulmonary hypertension. Chest radiography was performed in the posterior-anterior (PA) position. Cardiothoracic ratio, cardiac chamber enlargement, and the presence or absence of pulmonary arch prominence were reported by a single radiologist. Radiographs of patients with pulmonary hypertension obviously showed right ventricular and atrial enlargement and pulmonary arch prominence. The Echocardiography machine used in this study was a Medison V10 model that was made in Korea. Echocardiographic findings were observed, including tricuspid regurgitation (TR), Pulmonary Regurgitation (PR), Pulmonary Artery Acceleration Time (PAAT), systolic and diastolic ventricular dysfunction, the presence or absence of restrictive cardiomyopathy, and left ventricular (LV) mass index. Also, several variables were evaluated, such as mean volume of transfused blood over the past year, mean serum ferritin level over the past year, and a history of chelation therapy. Then, the patients' body surface areas and the LV masses were calculated.

Each patient who had a TR gradient greater than 25 mmHg was considered to have pulmonary hypertension. In every patient without pulmonary stenosis, the TR gradient plus the right atrium systolic pressure (RASP) was equal to the pulmonary artery systolic pressure (PASP) (PASP = TR+RASP). In patients without severe pulmonary hypertension, the RASP value was considered to be 5 mmHg, and, in pulmonary hypertension cases, the value is considered to be about 10-15 mmHg. Pulmonary artery systolic pressure (PASP) was calculated using the Bernoulli formula, i.e., 4(TRV)2(m/s)2+RASP. The data that were obtained were analyzed statistically with SPSS software, version 11.5 (SPSS, Inc. Chicago, Illinois, United States of America). We used the chi-squared test and Fisher's exact test to determine the association between the variables. To compare the averages in the two groups, the independent samples t-test or the Mann-Whitney test was used. All patients with congenital heart lesions were excluded from the study.

3. Results

In this study, 41 patients with thalassemia intermedia were studied, including 19 males (46%) and 22 females (54%). Ten patients (24%), including six males and four females, had pulmonary hypertension. There was no significant difference in patients with and without pulmonary hypertension among the males and females (p=0.264). Also, there was no significant difference between the two groups (with and without pulmonary hypertension) regarding patients' average ages (p=0.11), their mean age at the time of diagnosis (p=0.26) and at the time of transfusion (p=0.74), their mean level of serum ferritin (p=0.45), and hemoglobin (p=0.87) over the past year, PAAT (Pulmonary Artery Acceleration Time) (p=0.61), Mean pulmonary regurgitation gradient (Pulmonary Regurgitation) (p=0.58), and LV Mass Index (p=0.45) (Table 1).

Table 1. Distribution of prevalence of different variables in patients with and without pulmonary hypertension

Variables	Total population	With pulmonary hypertension	Without pulmonary hypertension
Mean age (year)	21.93±8.34	25.6±9.3	20.74±7.81
Mean age at time of diagnosis (year)	8.57±5.55	10.3±8.96	8±3.9
Mean age at time of transfusion (year)	9.97±7.11	10.6±9.44	9.73±6.21
Mean hemoglobin level over the past year (gr/dl)	9.18±1,11	9.13±1.21	9.20±1.42
Mean serum ferritin level over the past year (ng/ml)	1235.89±883.23	1001.60±753.6	1329±927.45
Pulmonary Artery Acceleration Time (ms)	124.51±28.53	119.9±27.64	126±29.1
Pulmonary Regurgitation gradient (mmHg)	10.6±4.23	8.9±6.17	6.19±5.57
LV Mass index	117.56±39.91	119.74±24.57	116.86±44.05

Of the 15 patients with a history of splenectomy, five (33%) had pulmonary hypertension. Five out of 26 patients (19%) with no history of splenectomy had pulmonary hypertension. Thus, splenectomy did not seem to cause any statistically significant difference between the two groups (p=0.453). Having undergone regular, irregular, or no blood transfusions made no significant difference in the two groups in terms of average LV mass index (p=0.337); Likewise, having received regular, irregular, or no chelation therapy did not make any significant difference between the groups in terms of the average LV mass index (p=0.220). No significant difference was observed

between the LV mass index, diastolic dysfunction, systolic dysfunction, or serum ferritin level, p=0.069, p=0.534, and p=0.31, respectively. However, there was a significant relationship between the two groups (with and without pulmonary hypertension) in terms of diastolic dysfunction (p=0.040). Diastolic dysfunction was observed in all ten patients with pulmonary hypertension; but there was no significant relationship between the two groups (with and without pulmonary hypertension) in terms of systolic dysfunction (p=1.000). None of the 10 patients with pulmonary hypertension had systolic dysfunction. Diastolic dysfunction did not have any significant relationship with blood transfusion (or lack of it) or chelation therapy (or its absence), p=0.679 and p=1.000, respectively. Similarly, systolic dysfunction had no significant relationship with blood transfusion (or lack of it) or chelation therapy (or its absence), p=0.759 and p=0.664, respectively. The difference in the mean serum ferritin levels between the two groups, with and without systolic and diastolic dysfunction, was not statistically significant, p=0.228 and p=0.486, respectively.

The prevalence rates of restrictive cardiomyopathy disorder between the two groups with and without pulmonary hypertension were statistically significant (p=0.007). Eight out of 10 patients (80%) with pulmonary hypertension had restrictive CMP, but only 8 out of 31 patients (26%) without pulmonary hypertension had restrictive CMP. Clearly, restrictive cardiomyopathy was more prevalent in patients with pulmonary hypertension.

4. Discussion

PAH is a frequent and life-threatening complication of hemoglobinopathies, such as thalassemia (2, 4, 7-9). Previous researchers have proposed that PAH is the main cause of heart failure in patients with thalassemia. The pathophysiology of PAH might be chronic anemia combined with oxidative stress due to hemolysis (4). Although thalassemia intermedia is milder than thalassemia major, it primarily can involve the heart and cause congestive heart failure. We determined the prevalence of PAH in thalassemia intermedia patients. The incidence of pulmonary hypertension in our study was 24%, and this severe complication of thalassemia intermedia was estimated to be 20.4% in a study of patients in northern Iraq (10). The incidence of PAH has been reported in a wide range, from 18.5 to 60% (2, 11-13). This variation might be due to the sample size and the patients' characteristics, especially their ages. However, there are different methods of investigating PAH that have different sensitivity and specificity, and these differences also could affect the reported PAH rate. Some authors believe that right heart catheterization, not just echocardiography (11), is the definitive method of determining pulmonary hypertension, but we chose to use echocardiography to diagnose PAH.

Hemolysis leads to release fragmented hemoglobin and activated NO as an intrinsic vasodilator (4, 7). Our results showed that, although more patients with splenectomy develop PAH, this association could not be confirmed statistically. Intravascular hemolysis increases after splenectomy and could worsen or promote PAH (11). There is some evidence about the role of splenectomy in platelet activation and developing pulmonary microthrombosis and blood cell adhesion to microvesicles' endothelia (4, 11). In 2014, Derchi proposed that advanced age and splenectomy are risk factors for pulmonary hypertension in patients with thalassemia intermedia (11). In Atichartakarn's study in 2014, the incidence rate of pulmonary hypertension in patients with thalassemia intermedia who had undergone splenectomies was reported to be 52.5%, which was higher than our findings (36.5%) (14). In previous studies, a correlation was proposed between the intensity of thalassemia and PAH. However, some studies, such as Machado's study, have suggested that developing abnormal pulmonary function is an age-related complication in hemoglobinopathies (9).

There are positive and negative theories about the role of regular blood transfusion in preventing pulmonary hypertension. For example, Chueamuangphan and Aessopos emphasized the benefits of blood transfusion (15, 16). Our results did not support the idea that transfusions have an effective role in preventing PAH. The severity of the disease and the hemoglobin level are the predisposing factors for determining the transfusion needs associated with PAH. In our study, the mean hemoglobin level over the past year was similar to that in Aessopos's study (9.1±1.1 gr/dl) (3). The mean serum ferritin level over the past year was 1235.89±883.2 ng/ml, and, in Aessopos's study, it was 1657±1477 ng/ml (3). There was no significant relationship between the average serum ferritin level and pulmonary hypertension. However, the serum ferritin level was less than 1000 ng/ml in 75% of patients with normal diastolic function. Therefore, maintaining the serum ferritin level below 1000 ng/ml can be an important factor in preventing the progression of diastolic dysfunction. In this study, 100% of patients with systolic dysfunction had serum ferritin levels greater than 1000 ng/ml. Thus, keeping the serum ferritin level below 1000 ng/ml is significant for preventing systolic dysfunction as well. In order for these results to be generalizable, more patients with systolic dysfunction should be studied, and the relationship between systolic dysfunction and serum ferritin level should be

examined further. In our study, there was no significant difference between mean PAAT (Pulmonary Artery Acceleration Time) in patients with and without pulmonary hypertension, so PAAT is not a useful index for diagnosing pulmonary hypertension.

In Aessopos's study, 34.5% of patients had pericardial thickening with or without effusion (3), whereas, in our study, pericardial thickening with or without effusion was not observed in any of the patients. All patients in Aessopos's study had normal left ventricular contraction (3). Our patients also had no systolic dysfunction. The mean LV mass index in patients was 117.56±39.91 (about three to five times greater than normal people have), but no significant relationship was observed between the two groups with and without pulmonary hypertension. Eighty percent of patients with pulmonary hypertension had LV mass indexes greater than 100, and 20% of them had LV mass indexes less than 100. In patients without pulmonary hypertension, 65% had LV mass indexes greater than 100, and 35% of them had LV mass indexes less than100. Therefore, if more patients had been included in the study, maybe we could have found a significant relationship between pulmonary hypertension and the increase in the LV mass index. The LV mass index was less than 100 for 47% of the patients who had received regular chelation therapy and for 28% of those who had not. Perhaps regular blood transfusions in patients who receive regular iron chelation therapy account for the decrease in the values of their LV mass indexes. There was diastolic dysfunction in 77% of those who did not receive chelation therapy or who received irregular chelation therapy. As a result, receiving irregular chelation therapy or not receiving the therapy could be a factor in the incidence of diastolic dysfunction. One of the most important findings of this study was that there was a significant relationship between the two groups (with and without pulmonary hypertension) in terms of diastolic dysfunction ($p=0.040$). All of the patients in the study who had pulmonary hypertension had diastolic dysfunction. Another finding was that there was a significant relationship between the two groups in terms of restrictive cardiomyopathy; 80% of patients with pulmonary hypertension had this disorder.

5. Conclusions

Our findings demonstrated that pulmonary hypertension occurs in 24% of patients with thalassemia intermedia and that PAAT is not a practical method for its diagnosis. The values of LV mass index were remarkably increased in these patients (three to five times greater than the normal population). Higher values of LV mass index were associated with PAH. Also, ferritin levels less than 1000 ng/ml was another indicator of systolic and diastolic dysfunction. Our recommendations are that 1) long-term follow up studies should be conducted in order to track patients and their prognoses; 2) given the high prevalence of pulmonary hypertension in patients with thalassemia intermedia, more regular programs should be designed and implemented for serial monitoring of patients by echocardiography and measurement of serum ferritin and hemoglobin levels; and 3) since it is common to see increases in the LV mass index in patients with thalassemia intermedia, further studies should be conducted on this cardiac index, and approaches should be developed to lower the index and to reduce the complications it causes later.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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