β-Thalassemia intermedia: morbidity uncovered

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Risk factors for pulmonary hypertension in patients with β thalassemia intermedia

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ABSTRACT

Background: Pulmonary hypertension (PHT) is a common yet poorly understood complication of β thalassemia intermedia (TI).
Methods: We herein evaluated risk factors for PHT in TI, through comparing 64 TI patients with evidence of PHT by symptomatology and echocardiography (Group I) to age- and sex-matched TI patients without PHT (Group II). Retrieved data included demographics, laboratory parameters, clinical characteristics, and received treatments that may influence PHT development; and reflected the period prior to PHT occurrence in Group I.
Results: The mean age of Group I patients at development of PHT was 37.3 ± 10.6 years; with 44% being males. Among studied parameters, Group I patients were more likely to be splenectomized (4.9-times), transfusion-naive (3.5-times); hydroxyurea-naive (2.6-times), or iron chelation-naive (2.3-times); and have nucleated red blood cell count $\geq 300 \times 10^6$/l (2.59-times) or a previous history of thromboembolic events (3.69-times).
Conclusion: TI patients who eventually develop PHT may be identified early on by being splenectomized, having high nucleated red blood cell counts and a previous history of thromboembolism. Prospective clinical trials that evaluate the efficacy, safety, and cost effectiveness of transfusion, iron chelation, and hydroxyurea therapy in preventing PHT in TI are invited.

1. Introduction

The term β thalassemia intermedia (TI) was first suggested to describe patients who have a milder anemia compared to patients with β thalassemia major, and who usually present to medical attention later in childhood and remain largely transfusion independent. However, it is now recognized that the diagnosis of TI carries higher morbidity than previously recognized [1]. Three main factors lead to the clinical sequelae of TI, ineffective erythropoiesis, chronic anemia/hemolysis, and iron overload secondary to increased intestinal absorption [2,3]. The extreme diversity in phenotypic expression in TI patients results in a wide variation in observed clinical complications [1]. Among the clinical complications of TI that was found to occur at a relatively high frequency, especially compared to patients with thalassemia major, is pulmonary hypertension (PHT) [1,3–7]. Significant advances have been made toward understanding the pathophysiology, diagnostic challenges, morbidity, mortality, and optimal management of PHT in patients with other hemoglobinopathies, namely sickle cell anemia [8]; however, data on patients with TI is limited. Chronic anemia and hypoxia [7], iron overload [9,10], splenectomy [11,12], hypercoagulability [13], and chronic hemolysis [4] have all been implicated in the pathophysiology of PHT in TI. PHT is neither associated with myocardial siderosis [14,15] nor left ventricular dysfunction in TI, but is a leading cause of right-sided heart failure and thus warrants attention [6,9,16].

In this study, we aim to demonstrate risk factors for PHT in patients with TI, in an effort to further understand the mechanism behind this potentially disabling complication, and to highlight those patients that carry a high-risk of developing PHT and deserve consideration for preventive strategies.

2. Materials and methods

This was a retrospective review of data collected on 584 patients with TI currently registered at six comprehensive care centers in

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Egypt, Iran, Italy, Lebanon, Oman, and the United Arab Emirates. Institutional review boards at each center approved the study protocol. An age of diagnosis beyond 2 years, hemoglobin values maintained between 7 and 9 g/dl without the need for regular transfusional regimen, with or without splenomegaly, were the main criteria to define the TI phenotype on presentation [17]. It should be mentioned, however, that transfusion may be later undertaken for many patients with TI when if the disease worsens as they grow older or after developing complications. Patients had the following β globin gene mutations: IVS-I-6 (T→C), IVS-I-5 (G→C), IVS-II-1 (G→A), or Codon 39 (C→T). None of the patients had Hb S, C, E/β or δβ thalassemia. Two Groups of patients were assigned: Group I (n = 64), TI patients with documented PHT defined as a systolic pulmonary artery pressure greater than 35 mm Hg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of >2.8 m/s + exertional dyspnea without evidence of left heart disease [18]; and Group II (n = 64), age- and sex-matched TI patients without PHT. For matching, we used the age at development of PHT in Group I, and matched patients from Group II. That age was considered the last patient follow-up and all retrieved data reflected the preceding period. Retrieved data included: demographics (age and gender); splenectomy status; history of heart failure (modified Framingham criteria [19]); history of previous thromboembolic events; history of thrombophilia (factor V Leiden, factor II [prothrombin] *G20210A*, or methylenetetrahydrofolate reductase *C677T* mutations, antithrombin III, protein C, or protein S deficiency); use of blood transfusions, iron chelation, hydroxyurea, antiplatelet or anticoagulant therapy; mean total hemoglobin level (pre-transfusion in transfused patients), fetal hemoglobin level, serum ferritin level, nucleated red blood cell count, and platelet count of all available laboratory records for each patient.

2.1. Statistical analysis

Descriptive statistics are expressed as means ± standard deviation (SD) or percentages where appropriate. Bivariate analysis was performed to determine differences in study parameters between the two Groups using the independent sample *t*-test for continuous variables and the Chi-square and Fisher's exact tests for categorical variables. Multivariate logistic regression analysis, using forward-stepwise selection, was done to determine the independent effect of study parameters. $P \leq 0.1$ was used as the criterion for inclusion into the model and a $P \geq 0.05$ was used for exclusion, where all significant variables on univariate analysis were entered into the model. In the multivariate model, nucleated red blood cell counts were categorized as < or $\geq 300 \times 10^6$/l and platelet counts were categorized as < or $\geq 500 \times 10^9$/l. All *P*-values are two sided with the level of significance set at <0.05.

3. Results

A total of 64 patients with documented PHT (Group I) were identified. The mean age at PHT diagnosis was 37.3 ± 10.6 years; with 44% being males. The mean age of matched patients without PHT (Group II, n = 64) was 37.9 ± 11.4; with 44% being males.

The mean serum ferritin level was higher in Group I compared to Group II (1233.2 ± 499.2 vs. 654.7 ± 234.5 ng/ml; $P = 0.01$). Moreover, the mean nucleated red blood cell count was higher in Group I compared to Group II patients (354.2 ± 199.2 vs. 214.7 ± 94.5 × 10^6/l; $P = 0.03$). A higher proportion of patients was splenectomized (84.4% vs. 46.9%; $P<0.001$) or had a previous history of thromboembolic events (40.6% vs. 7.8%; $P<0.001$) in Group I compared to Group II patients. Conversely, a higher proportion of patients received transfusion (78.1% vs. 56.2%; $P<0.001$), iron chelation (62.5% vs. 37.5%; $P<0.001$), and hydroxyurea (34.4% vs. 17.2%; $P<0.001$) therapy in Group II compared to Group I patients. There were no statistically significant differences between both groups with regards to other parameters (Table 1). Moreover, there was no statistically significant difference between Groups I and II in the proportion of patients with co-inheritance of α thalassemia [α^+ (-$\alpha^{3.7}$ and -$\alpha^{4.2}$) or α^0 (–^{Med} and –^{SEA})] or determinants associated with increased γ-chain production [*Xmn*-I +/+ genotype at position −158 of *HBG2*] (data not shown in Table 1).

Multivariate logistic regression analysis revealed that patients in Group I are more likely to be splenectomized (adjusted odds ratio [AOR]: 4.9, 95% confidence interval [CI]: 1.9–8.5); transfusion-naive (AOR: 3.5, 95% CI: 2.1–6.25); hydroxyurea-naive (AOR: 2.6, 95% CI: 1.1–5.25) or iron chelation-naive (AOR: 2.3, 95% CI: 1.2–4.25); and have NRBC count $\geq 300 \times 10^6$/l (AOR: 2.59, 95% CI: 1.69–6.05) or a previous history of thromboembolic events (AOR: 3.69, 95% CI: 2.38–7.05) (Table 2).

4. Discussion

Our study indicates that TI patients who develop PHT are characterized by being splenectomized, having high nucleated red blood cell counts and a previous history of thromboembolic events. Moreover, it suggests a potential role for transfusion, iron chelation, or hydroxyurea therapy in lowering the risk of PHT in patients with TI. These findings have important implications in understanding the pathophysiology of PHT in patients with TI, and pave the way towards the development of preventive and management strategies.

Table 1
Comparison of study parameters between Group I and Group II patients.

Parameter	Group I Pulmonary hypertension n = 64	Group II No pulmonary hypertension n = 64	*P*-value
Mean age ± SD, years	37.3 ± 10.6	37.9 ± 11.4	NS
Male, n (%)	28 (44)	28 (44)	NS
Mean total hemoglobin ± SD, g/dl	9.0 ± 1.3	8.8 ± 1.2	NS
Mean fetal hemoglobin ± SD,%	46.9 ± 27.0	52.4 ± 31.4	NS
Mean serum ferritin ± SD, ng/ml	1233.2 ± 499.2	654.7 ± 234.5	0.01
Mean nucleated red blood cell count ± SD, × 10^6/l	354.2 ± 199.2	214.7 ± 95.4	0.03
Mean platelet count ± SD, × 10^9/l	616.6 ± 197.4	556.3 ± 144.7	NS
Splenectomized, n (%)	54 (84.4)	30 (46.9)	<0.001
Heart failure, n (%)	3 (4.7)	2 (3.1)	NS
Previous thromboembolic events, n (%)	26 (40.6)	5 (7.8)	<0.001
Thrombophilia, n (%)	3 (4.7)	2 (3.1)	NS
Transfused, n (%)	36 (56.2)	50 (78.1)	<0.001
Iron chelation therapy, n (%)	24 (37.5)	40 (62.5)	<0.001
Antiplatelet or anticoagulant use, n (%)	3 (4.7)	2 (3.1)	NS
Hydroxyurea use, n (%)	11 (17.2)	22 (34.4)	<0.001

NS = non significant ($P \geq 0.05$).

Table 2
Multivariate analysis of parameters that differentiate patients with (Group I) and without pulmonary hypertension (Group II).

Parameter	Group II Referent	Group I AOR	95% CI	*P*-value
Splenectomized	1.00	4.90	1.90–8.50	<0.001
Nucleated red blood cell count $\geq 300\times10^6$/l	1.00	2.59	1.69–6.05	0.010
Splenectomized	1.00	3.21	1.29–6.55	0.007
Non-splenectomized	1.00	1.13	1.09–2.05	0.047
Previous thromboembolic events	1.00	3.69	2.38–7.05	0.020
Splenectomized	1.00	4.20	1.78–9.16	0.011
Non-splenectomized	1.00	2.11	1.03–7.44	0.049
Transfusion naivety	1.00	3.50	2.10–6.25	0.001
Splenectomized	1.00	4.00	1.18–8.45	0.004
Non-splenectomized	1.00	1.37	1.04–1.99	0.049
Iron chelation naivety	1.00	2.30	1.20–4.25	0.001
Splenectomized	1.00	1.12	1.01–3.32	0.038
Non-splenectomized	1.00	2.26	1.33–3.67	0.001
Hydroxyurea naivety	1.00	2.60	1.10–5.25	<0.001
Splenectomized	1.00	2.20	1.35–2.98	0.003
Non-splenectomized	1.00	1.22	1.02–1.99	0.044

AOR = adjusted odds ratio; CI = confidence interval.

A hypercoagulable state in patients with thalassemia has been established [20]. Ineffective erythropoiesis, in combination with premature intra- and extravascular hemolysis, lead to the emergence of damaged, prothrombotic red blood cells in the circulation of TI patients. Hemolysis causes iron-dependent oxidation of membrane proteins and formation of red-cell senescence antigens such as phosphatidylserine that cause thalassemic red blood cells to be rigid and deformed and to aggregate, resulting in premature cell removal [21–24]. Studies have shown that thalassemic red blood cells, through being a source of negatively charged phospholipids, can eventually increase thrombin generation [25,26]. An even higher number of circulating red blood cells with prothrombotic potential were found in splenectomized patients [27]. This justifies the high rate of thromboembolic events, especially in splenectomized patients with TI [1,28–32]. It should be noted that prothrombotic mutations do not play a role in the hypercoagulability of thalassemia [33,34]. Hypercoagulability, secondary to the aforementioned hemolysis and other established risk factors [35], and subsequent pulmonary vasculature thrombosis or embolism may explain the occurrence of PHT in TI [13], but need further evaluation. Of note, autopsies of a large series of patients with TI revealed thrombotic lesions in the pulmonary arteries, which may have been due to circulating platelet aggregates [36]. Similar findings of multiple microthrombi, which were composed mainly of platelets, were seen in the pulmonary arterioles and microcirculation in autopsies of two splenectomized patients with thalassemia [37]. A high rate of PHT in splenectomized TI patients has been documented and attributed to a chronic thromboembolic state [12,38]. Moreover, elevated levels of circulating red blood cell-derived microparticles were detected in splenectomized patients with TI [39]. Whether they contribute to the development of PHT in this patient population merits an evaluation.

Transfusion therapy was associated with a lower rate of PHT. In previous years, the prevailing approach has been avoidance of early blood transfusions and the concomitant requirement for chelation therapy in patients with TI through splenectomy, reserving the introduction of transfusion until later in the disease course when complications manifest. However, collective evidence now recommends avoidance or delay of splenectomy because of a multitude of associated complications, and an increasing evidence for a beneficial role of transfusions [1]. Observational studies continue to document a lower occurrence of thromboembolic events and PHT in transfused compared to transfusion-independent patients with TI [1,30,31,40]. Our results confirm these findings, which may be attributed to the potential role of transfusions in correcting the underlying ineffective erythropoiesis and the resulting damaged red blood cells with thrombogenic potential [41]. Although the suggestion of earlier introduction of blood transfusions will increase the rate of iron accumulation in TI patients, effective methods of iron chelation are now available [42]. In fact, iron chelation therapy was independently associated with a lower rate of PHT in our study. How iron overload can contribute to vascular disease in patients with TI is not completely understood. One previous study demonstrated a correlation between elevated liver iron concentration and PHT in TI; suggesting that PHT is strongly affected by iron overload and is not merely a consequence of the chronic hypoxic damage that progresses with age [9].

Fetal hemoglobin inducing agents like decitabine and hydroxyurea were shown to lower plasma markers of thrombin generation [35]. Hydroxyurea may modulate hypercoagulability in several ways, it may reduce phospholipid expression on the surface of red blood cells and platelets, and decrease red blood cell adhesion to thrombospondin, a thrombin sensitive protein [35]. It may also decrease leukocyte count, particularly monocytes expressing tissue factor, in addition to being a nitric oxide donor [37]. Thus, it is likely that these mechanisms explain the lower risk of PHT attributed to hydroxyurea use in our patients, as well as in those reported in other studies [43].

One limitation in our study is the use of echocardiography instead of cardiac catheterization for the diagnosis of PHT which may increase the rate of false positive findings. However, our patients were mainly screened and diagnosed with PHT after presenting with exertional dyspnea with no evidence of left heart disease. Echocardiography is still the modality of choice used in many studies on thalassemia and sickle cell anemia relying on reports of good relationship between Doppler estimates and invasive measurements of pulmonary arterial pressure at baseline and after treatment [4,6,7,44,45].

In conclusion, our study demonstrated that TI patients who eventually develop PHT are most likely to be splenectomized, have high nucleated red blood cell counts and a previous history of thromboembolism. This calls for a review of splenectomy as a procedure of choice, especially with its potential role in increasing TI-related complications aside from the inherent risk of infection associated with the procedure. It also calls for prospective clinical trials that evaluate the efficacy, safety, and cost effectiveness of transfusion, iron chelation, and hydroxyurea therapy in preventing PHT in this patient population. Earlier introduction of transfusion and iron chelation therapy aimed at preventing the consequences of chronic hemolytic anemia may benefit TI patients by prevention, rather than palliation of late and irreversible complications. Rather than enforcing the regular transfusion and iron chelation regimens implemented in thalassemia major, blood transfusion and chelation therapy, if initiated in patients with TI will require closer monitoring and should be individually tailored to meet patient needs.

Learning points

- A history of splenectomy or thromboembolic events predicts future development of pulmonary hypertension in thalassemia intermedia patients.
- High nucleated red blood cell counts also characterize thalassemia intermedia patients who develop pulmonary hypertension.
- Transfusion, iron chelation, and hydroxyurea therapy seem to have a protective role against pulmonary hypertension in thalassemia intermedia, which deserve to be prospectively evaluated.

Conflict of interest statement

The authors have no conflicts of interest to disclose. This study did not receive external funding.

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