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Evaluation of the Prevalence of Pulmonary Hypertension in Thalassemia Intermedia

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Abstract: Pulmonary hypertension is a relatively common cardiac complication in thalassemia. The objective of this study was to assess the prevalence of it in patients with thalassemia intermedia, so that we could find a solution for ameliorating it in the future. This is a descriptive study on patients with thalassemia intermedia referring to Booali thalassemia research center, Sari, Iran. All patients who were more than 10 years of age and underwent echocardiography enrolled in the study. Some relevant variables such as age, sex, age of the onset of transfusion,, ... were recorded. Evaluation of PA pressure was done by a pediatric cardiologist based on pulsed Doppler echocardiography. All gathered data analyzed by SPSS13 using descriptive statistics, Pearson and spearman correlation coefficient and nonparametric tests. Fifty patients, ages 11-56 years (27.8±9.9) including 25 male and 25 female were screened by echocardiography. All the patients had normal LVEF and RVEF (equal or more than 65%). Eighteen (36%) had normal mean PA pressure (equal or less than 20 mm Hg). Thirty two (64%) had mild pulmonary hypertension (m PA pressure = 20-40 mm Hg). None of them had moderate and severe pulmonary hypertension. There was significant correlation between duration of hydroxyurea, age of splenectomy and PHT. As pulmonary hypertension is common among the thalassemia intermedia patients, it is therefore important to select, according to clinical and lab. data, patients with thalassemia who should receive transfusions and iron chelation early in life, so that this keeps the hemoglobin level near to normal and protect them from high cardiac output.

Key words: Pulmonary hypertension, thalassemia, thalassemia intermedia

INTRODUCTION

β-thlassemia are a group of genetically inherited disorders characterized by chronic hemolytic anemia of variable severity. The genetic heterogeneity of this disorder results in a wide spectrum of clinical phenotypes that may vary from mild chronic hemolysis to a severe transfusion dependent hemolytic anemia (Aessopos *et al*., 1995). It is divided into 3 subgroups including major, intermedia and minor (trait). Patients with â thlassemia major require intensive transfusion support to survive. Patients with β-thlassemia intermedia have a somewhat milder phenotype and can survive without transfusion. The terms β-thlassemia minor and trait describe asymptomatic heterozygote for β-thlassemia (Kasper *et al*., 2005). The most common complications are related to iron overload. The heart is the main site. Among these problems are left sided cardiac failure, arrhythmia, pericarditis, pulmonary hypertension and right sided cardiac failure (Aessopos *et al*., 1995). Pulmonary Hypertension (PHT) can result from chronic pulmonary hemosiderosis, recurrent respiratory tract infection, peculiar formation of the chest, the presence of extramedullary sites of hemopoiesis in the thoracic cavity, liver fibrosis and high cardiac output (Aessopos *et al*., 1995; Atichartakarn *et al*., 2004; Singer, *et al*., 2006). The incidence of PHT is 10% in thal. major and more than 50% in thal. Intermedia (Atichartakarn *et al*., 2004). In a study, 7 patients with thal. intermedia presenting with right heart failure secondary to PHT were reported, but it doesn't say anything about its real incidence among those patients (Aessopos *et al*., 1995). In another study dilated cardiomyopathy remained the leading cause of mortality among patients with thal. major and PHT was the principal cause of heart failure in thal. Intermedia (Hahalis *et al*., 2005).

PHT in thalassemia is a clinical picture less commonly reported, some evidence from the literature also suggest that it requires more investigation. We evaluated PHT in patients with thalassemia intermedia referring to Booali

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thalassemia research center in Sari, Iran, in order to determine its incidence, quantity, relation to some factors such as age, splenectomy, thalassemia faces and others. So that we could intervene appropriately and decline the level of morbidity and mortality.

MATERIALS AND METHODS

This is a descriptive and cross sectional study upon patients with thal. intermedia, seen regularly at Booali thalassemia research center in Sari, Iran. All patients who were more than 10 years of age and underwent echocardiography enrolled in the study. Age, sex, age of the onset of transfusion, spleen status, transfusion state, average 3 last hemoglobins, thalassemia facial status, cardiac clinical manifestations (palpitation, dyspnea, easy fatigability,…), associated complications (diabetes mellitus, cardiac or liver disease, thyroid or parathyroid hypofunction), drugs consuming status (hydroxyurea, desferal, deferiprone, ASA, folic acid, digoxin, captopril or enalapril, furosemide, progestrione, testosterone, calcium, …) were recorded.

Measurement of Pulmonary Artery (PA) pressure: Evaluation of PA pressure was done by a pediatric cardiologist based on pulsed Doppler using the device Vingmed 800 manufactured in Belgium. Tricuspid Regurgitation (TR) jet velocity (as pressure gradient) plus about 10 mmHg (as estimated RA systolic pressure) approximates PA systolic pressure. Pulmonary jet velocity (as pressure gradient) plus about 10 mm Hg (as estimated end diastolic RV pressure) accounts for PA diastolic pressure. The PA mean pressure measured by the equation:

$$PAP\ m = 90-(AT\times 0.62)$$

where, AT is the PA acceleration time obtained from pulsed Doppler echocardiography (Norman, 1993).

Pressure measurements were performed 3 times for each patient and then the average calculated. PHT (in our study) based on most references defined as mean PA pressure of more than 20 mm Hg (and systolic of more than 30 mm Hg, diastolic of more than 10 mm Hg) (Singer *et al*., 2006; Park, 1996), then divided into mild, moderate and severe according to mean PA pressure as: mild (20-39 mm Hg), moderate (40-54 mm Hg), severe (more than 54 mm Hg).

Severity of thalassemia determined based on the Table 1.

Table 1: Scoring of the severity of thalassemia

	Scoring		
Variables	0	1	2
Age of diagnosis (year)	>5	2-5	<2
Age of the onset of transfusion (year)	>6	1-5	<1
Spleen size (cm)	<8	8	>8
Facial changes	No	Moderate	Severe

Thalassemia intermedia: In this study defined as hemoglobin F of more than 50% but no need to frequent transfusion.

Cardiac disease: In this study, defined as consuming cardiac drugs (digoxin, furosemide, captopril or enalapril, amiodarone…) recommended by pediatric cardiology (according to echocardiographic results).

All gathered data analyzed by SPSS13 using descriptive statistics, Pearson and spearman correlation coefficient and nonparametric tests.

RESULTS AND DISCUSSION

Fifty patients, ages 11 to 56 years (27.8±9.9) including 25 male and 25 female were screened by echocardiography.

All patients' characteristics and hematologic data were showed in Table 2.

All the patients had normal LVEF and RVEF (equal or more than 65%). Eighteen (36%) had normal mean PA pressure (equal or less than 20 mmHg). Thirty two (64%) had mild pulmonary hypertension (m PA pressure = 20-40 mm Hg) (Fig. 1). None of them had moderate and severe pulmonary hypertension. Patients with mild pulmonary hypertension consisted of 15 (47%) male and 17 (53%) female, the youngest was 11 years old. Mean PA pressure in all patients was 24.7±6.9 (ranging 16-39). PA pressures were shown in Table 3. Correlation of some factors was determined. As shown in Table 4, there was no significant correlation between age, sex, age of diagnosis of thalassemia, age of splenectomy, dose of hydroxyurea, severity of thalassemia, ferritin and presence of PHT but there was significant correlation between duration of hydroxyurea, age of splenectomy and PHT. As shown, development of PHT increased no significantly with ferritin, severity of thalassemia and so on, which were not significant.

This study showed that 64% of our patients had mean PA pressure ranging 23-39 mm Hg while in Aessopos study all p atients had PA pressure ranging 35-60 mmHg (Aessopos *et al*., 1995). This is probably much higher than our patients' because of their older age, higher level of ferritin and more splenectomized patients

Table 2: Patients characteristics and hematologic data

Variables	Mean±SD (%)
Splenectomy	22 (44)
Severity of disease	
Mild	26 (56.2)
Moderate	18 (39.1)
Severe	2 (4.3)
Cardiac disease	8 (16.3)
Hypothyroid	5 (10.2)
Drugs	
HU	
Folic acid	45 (90)
ASA	44 (88)
Digoxin	24 (48)
Desferal	4 (8)
Estrogen	2 (4)
Progesterone	3 (6)
Testosterone	2 (4)
Captopril	1 (2)
Furosemide	0 (0)
Sildenafil	0 (0)
Others	0 (0)
Ca-D	27 (54)
Rocaltrol	
Inderal	
Age of diagnosis of thalassemia	12.1±10.5
Number of transfusion/age	8.5±6.9
Age of splenectomy (year)	16.7±7.9
Spleen size (size)	7.9±4.8
Hemoglobin(avge of 3 last Hb) (g dL^{-1})	9.8±0.93
Duration of hydroxyurea (year)	5.6±2.7
Dose of hydroxyurea (mg/kg/day)	11.5±3.3
Ferritin (avge during the last year) (ng mL^{-1})	646.0±419

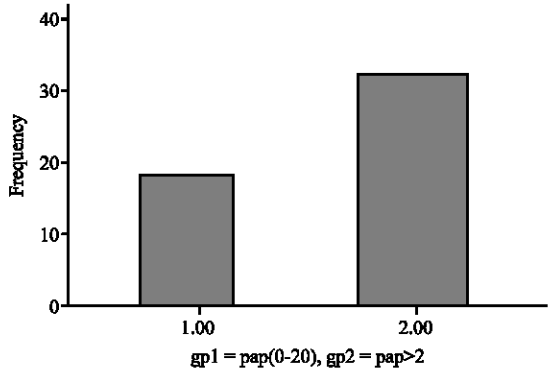

Fig. 1: Number of patients with normal PA pressure (gp = 1) and PHT (gp = 2)

which indicate more severity of their patients. In another study there was significant correlation between increased platelet activation, measured by P-selectin and PHT. Increased thrombin-antithrombin 3 level was more prevalent in the presence of PHT, but increased fibrinolysis or low protein C level was not (Singer *et al*., 2006). In the study of Hamdy, presence of RV systolic dysfunction was related to higher level of serum ferritin (Hamdy *et al*., 2004). This finding is not in the same direction with our study, probably because our patients were all of intermedia type and their ferritin were not very

Table 3: PA pressures of patients with PHT

PA pressures	Mean±SD	Range
Systolic PA pressure	40.8±7.8	(32-58)
Diastolic PA pressure	23.3±3.3	(19-30)
Mean PA pressure	28.8±5.1	(23-39)

Table 4: Correlation of some variables with presence of mean PHT

Variables	Correlation coefficient	p-value
Age	0.10	0.52
Age of diagnosis of thalassemia	0.05	0.70
Age of splenectomy	-0.48	0.02*
ferritin	0.27	0.08
Hydroxyurea (dose)	0.03	0.87
Hydroxyurea (duration)	0.38	0.009*
Sex	0.17	0.25
Severity of thalassemia	0.21	0.17
Presence of cardiac disease	0.10	0.54

*Significant

high. In Singer's (2006) study, there was positive correlation between age and splenectomy with pulmonary pressure . Another study acknowledged this finding too, as it showed the patients, among thalassemia intermedia or major, who required splenectomy had higher than normal pulmonary pressure, however this abnormalities remained unchanged after splenectomy. Nonetheless the removal of spleen may contribute to the prevention of further cardiac damage by ameliorating the hematological status and reducing the transfusion need (Aessopos *et al*., 2005). In our study, there was also a significant reverse correlation between age of splenectomy and presence of PHT that is in direction with the above studies. In this study there was a positive correlation between duration of hydroxyurea and presence of PHT, but it is not supported by literature (Rashidighader and Kousarian, 2006; Triadou *et al*., 1994), it is obvious that further studies are warranted.

In another study by Aessopos A, well-treated thalassemia major patients, in contrast to thalassemia intermedia patients, didn't develop PHT while systolic LV dysfunction was present only in thalassemia major cases. Assuming that PHT in β-thalassemia results from a rather complex pathophysiology, it was suggested that chronic tissue hypoxia seems to be a key role. Regular lifelong therapy in thlassemia patients eliminates chronic hypoxia, thereby preventing PHT, whereas the absence of systematic therapy in thalassemia intermedia leads to a cascade of reaction that compensates for chronic anemia but at the same time allow the development of PHT (Aessopos and Farmakis, 2005). In some other studies also acknowledge this conclusion, as PHT and RV dysfunction are also seen in thalassemia major patients who are iron overloaded (Merault *et al*., 2005; Koren *et al*., 1987). High cardiac output in patients with β-thalassemia is a compensatory mechanism to a number of factors. Anemia, low PO_2, altered O_2 delivery from

abnormal hemoglobin and low 2, 3 DPG in transfused blood results in tissue hypoxia that requires a state of high cardiac output which itself increases the pulmonary pressure in patients with a constricted pulmonary vascular bed arising from other factors such as hormonal, liver fibrosis, bone marrow expansions (Aessopos *et al*., 1995).

Considering those explanations, it is therefore important to select, according to clinical and lab. Data, patients with thalassemia who should receive transfusions and iron chelation early in life, so that this keeps the hemoglobin level near to normal and protect them from significant bone deformities and highly cardiac output. The prescription of antithrombotic agent (aspirin, dipyridamole) for patients who have undergone splenectomy is also recommended. It is obvious that, to clarify the issue of PHT and RV dysfunction in thalassemia further clinical trials are required.

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