EVIDENCE OF PULMONARY HYPERTENSION IN PATIENTS WITH THALASSEMIA MAJOR BY USING ECHOCARDIOGRAPHY

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ABSTRACT

Background

Thalassemia major is one of the most inherited disorders in the Middle East; it has many complications related to iron overload and hepatitis viral transmission; complication of iron overload has destructing effect on many organ systems including liver; heart; pancreas; and lung. In the lung lead to pulmonary arterial hypertension which is defined as pulmonary artery systolic pressure ≥25mmHg during rest.

Objectives

To detect the prevalence of pulmonary hypertension in patients with thalassemia major and how supportive measures affecting outcome of it.

Patients and Methods

A cross sectional study undertaken in Shaheid Hemn Teaching hospital, center for internal medicine diseases with collaboration of thalassemia center inside the hospital; 100 thalassemia major patients who are diagnosed previously by hemoglobin electrophoresis without any other comorbidity taken as a sample and echocardiography done using Phillips CX50 machine of 2009 model; the data then collected and using SPSS v23 for analyzing data.

Results

Study show 53% of thalassemia major has evidence of increased pulmonary artery pressure and only 1% has clinically significant pressure; splenectomy show high risk factor for occurrence of pulmonary hypertension but other supportive measures has no obstacle effect in its occurrence.

Conclusion

Most thalassemia major patients have evidence of pulmonary hypertension at least mild one; and putting splenectomy as a last line of managing them is recommended.

Keywords: *Thalassemia Major, Splenectomy, Pulmonary Hypertension, Echocardiography.*

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INTRODUCTION

Thalassaemia major (TM) is an inherited impairment of haemoglobin production, in which there is partial or complete failure to synthesise a specific type of globin chain [1]. Failure to synthesis beta chains (beta thalassaemia) is the most common type of thalassaemia [1], although prevalent in Mediterranean countries and in the Middle East, this disease has become a global health related problem due to increased immigration trends [2]. Heterozygotes have thalassemia minor, a condition in which there is usually mild anaemia and little or no clinical disability, which may be detected only when iron therapy for a mild microcytic anaemia fails [3]. Homozygotes (thalassemia major) either are unable to synthesise haemoglobin A or, at best, Produce very little; after the first 4–6 months of life, they develop profound hypochromic anaemia [1] .

The (β) cluster chromosome lies at chromosome 11p15.5 [3]. It is diagnosed by using Hb electrophoresis [2] which shows increase in production of fetal hemoglobin (HbF) rather than normal adult.

At present, we are dealing with an adult population of TM patients who may suffer from the side effects of long-term treatment—namely, transfusion-associated infections (particularly hepatitis B and C and, in some populations, HIV) and organ damage (liver, heart, endocrine glands) due to unsatisfactory long-term iron chelation [1].

The main cause of death in adult TM patients is still cardiac complications. Heart failure in these patients is multifactorial, involving chronic anemia, remaining iron overload, myocarditis, pericarditis, and probably many other mechanisms [1,3].

The development of pulmonary hypertension affects long-term prognosis in -thalassemia, but the underlying pathophysiology is incompletely understood. Several mechanisms have been proposed such as tissue hypoxia, causing endothelial dysfunction and a high-output state due to anemia [2].

By measuring tricuspid regurgitation and Doppler flow of the pulmonary artery, echocardiography has proved to be an accurate and reliable method to assess pulmonary artery pressure [4].

Echocardiography is a very accurate, widely available, and widely used imaging approach. However, the quality of images can be suboptimal because of poor tissue penetration (e.g., excessive adipose tissue, position of the lungs relative to the heart [3]. The relationship between the pressure gradient (ΔP) across a narrowing and the velocity (v) of blood flow is described by the simplified Bernoulli equation $\Delta P = 4v2$

This equation allows calculation of maximum and mean gradients across stenotic valves, estimation of pulmonary systolic pressure, and detailed evaluation of intracardiac hemodynamics with regurgitated valves.

The aim of this study is 2 parts; first to identify those with pulmonary arterial hypertension and second to identify the effect of treatment modalities on preventing pulmonary artery hypertension [5]. Despite the established link, the incidence of pulmonary hypertension in -thalassemia major has varied widely. Earlier studies reported a very high incidence (approx. 70–80%), but this figure was remarkably lower in more recent trials (approx. 10%)[2].

The normal pulmonary vasculature is a low-pressure system, with less than one tenth the resistance to flow observed in the systemic vasculature. Pulmonary hypertension refers to the hemodynamic state in which the pressure in the pulmonary artery is elevated above a mean of 25 mm Hg [3].

The syndrome of pulmonary arterial hypertension results when blood flow through the pulmonary circulation is restricted, thereby leading to pathologic increases in pulmonary vascular resistance and, ultimately, to right ventricular failure and early death[3].

Causes of pulmonary arterial hypertension is frequent but chronic hemolytic state is one of the causes beside to idiopathic connective tissue diseases and drugs … etc. Pulmonary hypertension (PHT), which is a chronic process attributed to many factors: -First, the chronic anemia leads to increased cardiac output and pulmonary blood flow, resulting in pulmonary vasoconstriction.

-Second, the hypoxemia, the chronic pulmonary hemosiderosis, and the hypersensitivity reaction to Deferoxamine therapy can cause arterial fibrosis and increased pulmonary vascular resistance.

-Third, the hypercoagulable state secondary to increased platelet counts following splenectomy may restrict the pulmonary vascular bed [6].

The gold standard for diagnosing pulmonary hypertension is a right heart catheterization (RHC) and measurement of blood pressure in the pulmonary arteries. Although RHC is now a relatively safe

procedure, it is invasive and impractical to perform in patients for whom it is not clearly indicated. Because it is non-invasive, widely available and relatively inexpensive, echocardiography is frequently used to screen for PH, monitor progression over time and allow identification of patients for whom diagnostic RHC is warranted [7].

The aim of the study is to detect patients with thalassemia major that have pulmonary hypertension and to determine the role of supportive measures in preventing the occurrence of pulmonary hypertension.

PATIENTS AND METHODS

In the thalassemia center in Sulaimai Internal Medicine Hospital, we collect 100 cases of beta thalassemia major randomly whom previously diagnosed by Hb electrophoresis as a study sample between November and December 2017 for assessing pulmonary artery systolic pressure; all of them have no other comorbidities that interfere with pulmonary artery pressure; excluding patients with thalassemia minor and intermedia; the echocardiography done by single person using tricuspid regurjetant velocity to determine right atrial pressure adding to response of inferior vena caval response to deep inspiration.

We exclude patient with accidental abnormal echo finding trying not to interfere with our results.

Echocardiographic method

We used Phillips CX50 model 2009 machine in our study and we set a criteria as mentioned before for assessing the patients; first by 2D echo in left parasternal view inspecting heart generally try to found any excluding criteria; then in apical 4 chamber view in Doppler mode measuring tricuspid regurjetant velocity in square multiplied by 4; we used 25 mmHg as borderline pressure as defined and pressure more than 50 mmHg as clinically significant pulmonary hypertension this is based on practical guideline [2].

Statistical analysiswas done by using SPSS v23.

RESULTS

As shown in table (1) 100 patients were collected divided nearly equal between male and female 47 and 53 respectively and their age between 10-44 years A p value of ≤ 0.05 regarded as statistically significant finding; 44% of theme did splenectomy while the remaining did not and 100% receiving folic acid as supportive measures; 95% on regular transfusion, while only 5% not; 99% receiving chelating therapy in the form of tablet Deferiprone and only 1% didn't receive due to hypersensitivity reaction.

Table 1 show the numbers of our variable which is age ; sex; splenectomy; folic acid; transfusion and chelating therapy and corresponding their numbers.

In table 2, we make a chronological and sexual comparison of patients and shows PASP increase with increasing age and vice versa but it is statistically not significant which may be due to sample size; at the same time, there is no difference in PASP according to sex but this was statistically not significant.

Table 3 shows the comparison of age and gender in regard to pulmonary artery systolic pressure.

Table 4 shosw huge relation of splenectomy to increasing PASP which is theoretically one of important risk factors with a p value of 0.005 that's statistically significant.

In table 5 we want to show the effect of the supportive and preventive measures on decreasing PASP; all of them on folic acid, that's why we cannot depend on it for statistical purposes here to show any significant; good transfusion program which is every 21 days in our patients show decrease occurrence of PASP but statistically not significant; yet the chelation therapy which is not used by the only patients show huge increase in PASP but statistically also not significant.

Figure 1. Show the correlation between age and PASP in which there is progressive increase in PASP with age of the patients which is not a physiological response in normal adult person this is may be due to effect of iron overload also but has not statistical significance.

Table 1. Variables and their numbers

Variable	N (%)
Age groups (years)	
10-20	34 (34)
21-30	48 (48)
More than 30	18 (18)
Sex	
Male	47 (47)
Female	53 (53)
Splenectomy	
Yes	44 (44)
No	56 (56)
Folic acid	
Yes	100 (100)
No	0 (0.0)
Transfusion	
Yes	95 (95)
No	5 (5)
Chelation therapy	
Yes	99 (99)
No	1 (1.0)

Table 2. Total numbers with significant high PASP i.e. ≥50mmHg

PASP	N (%)
≥ 50 mmHg	1%
≤50 mmHg	99%

This table shows that only one patient have PASP ≥ 50mmHg and his age is 44 year old man.

Table 3. Comparison of age and gender in regard to pulmonary artery systolic pressure.

Participants	N (%)	PASP (mean± SD)	P value
Age groups (years)			
11-20	35(35.3)	21.03±5.25	
21-30	47(47.5)	27.06±6.41	
More than 30	17(17.2)	33.44±8.63	0.098
Sex			
Male	47(47)	26.06±8.26	
Female	52(53)	25.97±7.32	0.947

Table 4. Association of pulmonary artery systolic pressure with splenectomy.

Splenectomy	PASP (mean± SD)	P value
Yes	28.45±8.63	0.005
No	24.09±6.4	

Table 5. The association of pulmonary artery systolic pressure with different supportive treatments.

Supportive treatments	N (%)	PASP (mean± SD)	P value
Folic acid			
Yes	100 (100)	26.02±7.74	N/A*
No	0 (0.0)	0.0±0.0	
Transfusion			
Yes	94 (94.9)	26.14±7.63	0.512
No	5 (5.1)	23.8±10.4	
Chelation therapy			
Yes	98 (99)	25.88±7.65	0.070
No	1 (1.0)	40.4±0.0	

*N/A: Not applicable

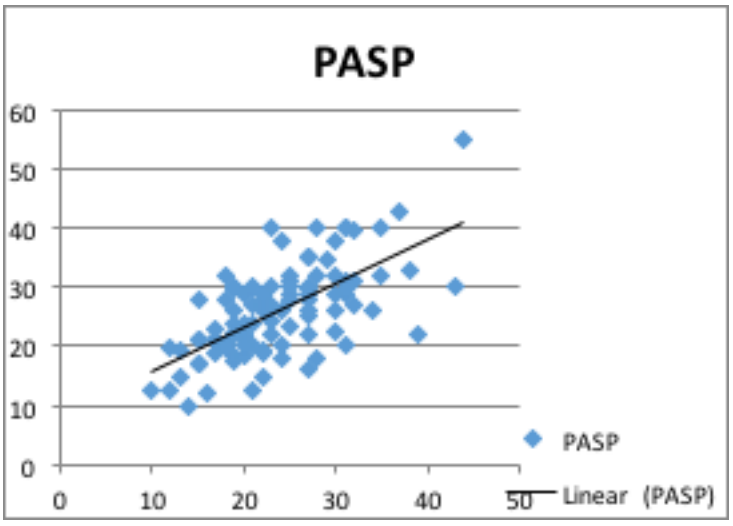

Figure 1. Liner correlation PASP with Age.

DISCUSSION

This study done in general medical hospital in collaboration with thalassemia center inside the hospital. The study showed that 47% of patients have pulmonary hypertension and the reminder has normal PASP; only one patient has pressure ≥ 50mmHg and he was man of 44 year Old. Our result is nearly comparable to some other studies in that way the most other study showed nearly 40% evidence of high PASP and nearly 1-2% clinically significant PASP.

In the study also shows no effect of folic acid on pulmonary pressure which may be due to increase production of abnormally shaped RBC or may be our sample size make this obstacle and in the other major studies showed the same effect and in other studies not concerned about it.

The study showed that splenectomy has crucial relation to high pulmonary pressure due to release of platelet and abnormal shaped RBC remain in circulation that leads to activation of coagulation cascade and microthromboemboli occur in pulmonary circulation and leads to secondary pulmonary hypertension and in the other studies also shows the good relation between splenectomy and high PASP.

The only patient who did not receive chelation therapy in the study has got high PASP but it shows that statistically not significant while in the most other studies concerning on it because it leads to decrease iron level and decreasing toxic effect of iron on different tissues including pulmonary vascular bed that error may be due to sample size.

Transfusion therapy theoretically should have; first beneficial effect due to decrease load on bone marrow and less abnormal shaped RBC produced which make coagulation cascade less activated; second increase iron overload and leads to more pulmonary vascular resistance; the study shows that those patients did not receive transfusion; mean PASP is lower than those who received it (23.8±10.4) and (26.14±7.63) respectively

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