Cardiac affection in pediatric patients with β- thalassemia major.

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Abstract :

Thalassemia is considered one of the most common monogenic diseases around the world with similar incidences in both genders.Transfusion-dependent thalassemia syndrome is associated with complications such as cardiomyopathy and pulmonary hypertension (PH) due to iron overload.

Aim of work : to detect cardiac affection early in beta-thalassemia major pediatrics.

Method: Echocardiography was done for 50 children with B-thalassemia major in comparison with another 50 children as a healthy control group , also echocardiography results were correlated with laboratory data of patients.

Conclusion: Significant high pulmonary artery pressure was detected in 38% of patients.

And impaired function was significantly associated with PAH while was not significantly correlated with serum ferritin.

Keywords ; beta thalassemia major ,PAH, iron overload.

Introduction

Thalassemia is the most common hemoglobinopathy in Egypt. Thalassemia has a high incidence of mortality and morbidity[(1)].

Patients with severe forms of B-TM first exhibit worsening anemia during

infancy and are transfusion dependent for life[2].This leads to iron overload and iron deposition in a number of parenchymal tissues including the heart resulting in ventricular systolic and diastolic dysfunction[3].

The most frequent complication in thalassemia patients that require specialized medical care is cardiovascular disease, especially in children and adolescents[4].

A known consequence of transfusion-dependent thalassemia syndrome is pulmonary hypertension (PH) and iron overload cardiomyopathy. Chronic hemolysis, iron overload brought on by frequent transfusion therapy, hypercoagulability, and modifications in circulating cells following splenectomy are some of the factors contributing to the multifactorial mechanism[5].

Aim of work : to do echocardiography in pediatric patients with B-thalassemia major and correlate results with laboratory data for early detection of cardiac affection in these patients .

subject and Methods ;

Study design:

Case-control study .

Systolic and diastolic dysfunction are late indicators of cardiac dysfunction in thalassemia patients, despite echocardiography being the usual method of assessing heart function.

Echocardiography study is the standard tool to monitor cardiac function in thalassemia patients yet systolic and diastolic dysfunction is late signs[6].

Thalassemia major patients have extensive asymptomatic periods with normal left ventricular (LV) function. Before symptoms manifest, early detection of ventricular dysfunction Because it highlights the necessity of chelator medication optimization, early detection of ventricular failure

before the onset of symptoms can change the prognosis of these individuals[7].

Study population and sampling

We included in this study, 50 thalassemia major pediatric patients who regularly followed up in the outpatient hematology clinic of Fayoum university hospital (group1) and compared them with 50 matched apparently healthy controls (group2). Each patient underwent clinical and echocardiographic evaluation.

Study setting:

This study was a hospital-based study, conducted in the Hematology_pediatric and Pediatric Cardiology Outpatient Clinics at Fayoum University Pediatric Hospital.

Inclusion criteria:

Children with thalassemia major.
Age :2-14 years .
Both gender.

Exclusion criteria:

Patients with congenital heart diseases.

Patients with rheumatic heart diseases.

Patients with hemoglobinopathy other than thalassemia.

All patients were subjected to the following:

• ***history taking***:

full history taking focusing on the history of preceding upper respiratory tract infection , fatigue ,dark urine, hemoglobinuria ,pallor and yellowish skin ,facial bone deformity ,anorexia , abdominal swelling , and history of drug intake.

***clinical examination* :**

Including:

1_General examination

4_Cardiac examination

5_Chest examination

6_Abdominal examination

• ***laboratory investigations*** *:*

1_CBC with Hb and reticulocyte count

2_ serum ferritin

3_serum iron

Echocardiography(ECHO)

1- A pediatric cardiologist conducted an ECHO study on all of the patients using a Vivid-5 color Doppler ultrasound echocardiography machine.

2- A complete echocardiographic examination was performed to exclude the presence of any primary cardiac diseases .

with great emphasis on left ventricular (LV) dimensions, right

ventricular (RV) dimensions, and left atrial (LA) dimensions.

3- Assessment of LV ejection fraction ;from the standard transthoracic windows, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), LV posterior wall (LVPW), and LV ejection fraction (EF) and fractional shortening (FS).

4- Assessment of LA diameter ,Ao diameter, and LA/Ro ratio .

5- Using continuous wave (CW) Doppler, tricuspid regurge (TR) peak signal velocity was assessed and pulmonary artery

pressure (PAP) so on using the simplified Bernoulli equation (P = 4(TRmax)2).

Ethical Consideration :

The Faculty of Medicine Research Ethical Committee examined this work. The researcher explained to the participants the goals of the study and the methods used for the examination and investigation. Additionally, they must respect the privacy of personal data and their freedom to decline to take part in the study.

Statistical Methods:

Statistical Package for Social Sciences was used for data handling (version 15.0; SPSS Inc., Chicago, IL, USA). The data were summarised using basic descriptive statistics, such as mean and standard deviation. Simple X2 tests were used to assess nominal data, independent sample tests were used to compare means between two groups of cases, and one-way analyses of variance were used to study data from more than two groups (ANOVA). P values less than 0.05 were regarded as significant probability values.

Results; ECHO showed that 38% of B-thalassemia major patients have pulmonary hypertension and 6% of them have impaired cardiac function.Many factors were correlated with pulmonary hypertension with significant correlation including age in years with (P =,054) and impaired cardiac function with (P=,022) ,while others had no correlation with PH including serum ferritin with (P=0.188), iron chelator intake with P=,597 and splenectomy with P=,975.

Serum ferritin level had no significant relation with PH and impaired function .

Table 1: Distribution of the beta thalassemia major patients according to gender and age.

variable		Cases (N=50)	
		Mean	**SD**
Age in years		7.4	3.3
		N	**%**
Sex	Male	26	52.0%
	Female	24	48.0%

52% of beta thalassemia major patients are males with a ratio 1,08 between males and females, age ranges from 2 to 14 with mean value 7,4 ± 3,3 SD**.**

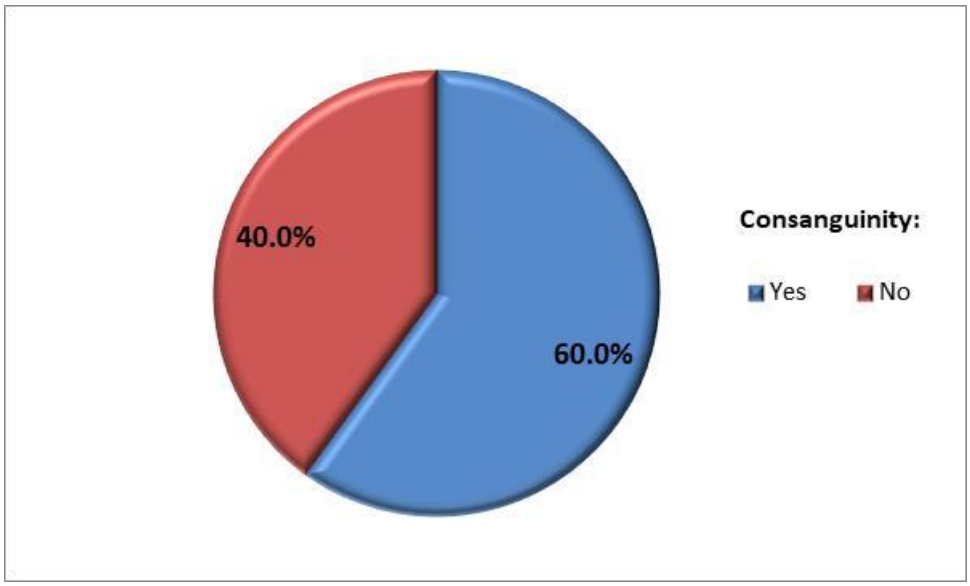

Figure 1:Distripution of B-TM patients according to consanguinity

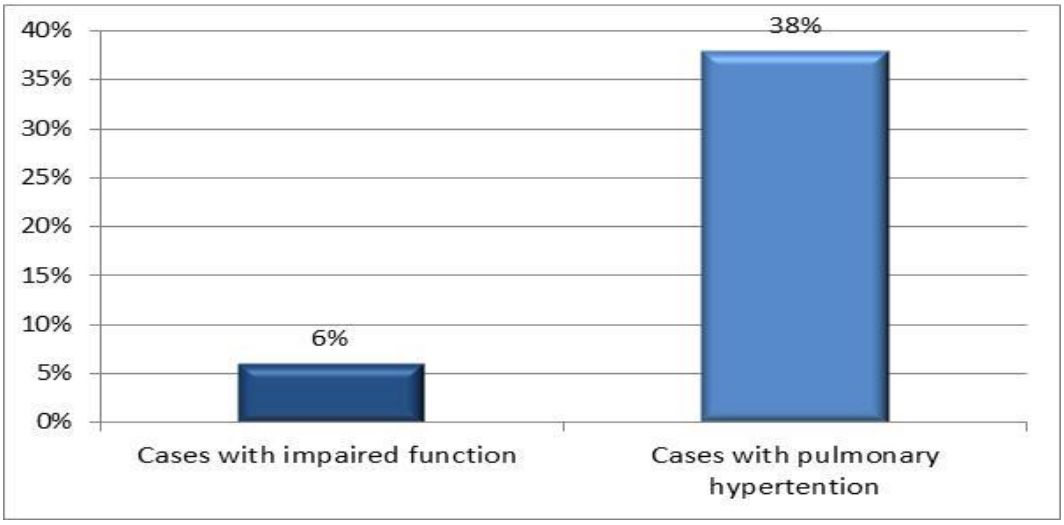

Figure 2;Distribution of B-TM patients according to impaired cardiac function and pulmonary hypertension

Table 2: Relation between socio-demographics and pulmonary hypertension

		Pulmonary hypertension		No pulmonary hypertension		P-value
		Mean	**SD**	**Mean**	**SD**	
Age in years		8.5	3.5	6.7	3.0	0.054
		N	**%**	**N**	**%**	**P-value**
Sex	Male	9	47.4%	17	54.8%	0.608
	Female	10	52.6%	14	45.2%	

According to this table ,there is a relation between the increased range of age in years and increased incidence of pulmonary hypertension while no significant correlation between gender and incidence of pulmonary hypertension.

Table 3: Relation between impaired function and pulmonary hypertension

variable		Pulmonary hypertension		No pulmonary hypertension		P-value
		N	%	N	%	
Impaired function	Yes	3	15.8%	0	0.0%	0.022*
	No	16	84.2%	31	100.0%	

This table shows a significant association between pulmonary hypertension and impaired cardiac function.

Table 4:Relation between splenectomy and pulmonary hypertension

Variable		Splenectomy		No splenectomy		P-value
		N	%	N	%	
Pulmonary hypertension	Yes	5	62.5%	26	61.9%	0.975
	No	3	37.5%	16	38.1%	

This table shows no correlation between splenectomy and pulmonary hypertension.

Discussion

Thalassemia is an autosomal recessive condition that affects both sexes equally frequently. Thalassemia's pathophysiology is mostly dependent on inefficient erythropoiesis. One of the most prevalent single-gene illnesses worldwide, it encompasses a spectrum of congenital hemolytic syndromes[(8)].

It has a high prevalence of mortality and morbidity, making it the most prevalent hemoglobin disorder in Egypt [(9).]

In Egypt, the carrier rate ranges from 5.3 to 9%, and out of the 1.5 million live births per year, approximately 1000 babies are thought to be born with -thalassemia major. In Egypt, the average annual financial cost of managing beta-thalassemia is estimated to be $10 million, and this expense is rising. There are 9912 patients with -thalassemia registered in the main Egyptian centers[(10).]

Out of 50 B-TM patients included in our study, 26 were males and 24 were females with a ratio of 1.08 between males and

females (***Table1)***. So,both genders are affected but with a slightly male predominance.This male predominance was shown in previous studies by ***Mannan et al.,2013 and laghari,et al,2018***[11],[12]**.**

60 % of B-TM patients included in this study were of consanguineous marriage and 44 % of patients had +ve family history (***figure 1)***.Our results support the role of inheritance in B-TM patients as shown in the study by ***Nasreen et al.,2010***[13]**.**

Echocardiographic examination for the 50 B-TM patients in this study showed that 38% of cases have pulmonary hypertension and 6% of them have impaired cardiac function**(*figure 2)*** .only the patients with impaired cardiac function presented with clinical symptoms during the examination as dyspnea and suffer from difficulty to make an ordinary effort while the majority of cases that detected during our study with cardiac affection have no cardiac symptoms ,this supports the high importance of both ECG and ECHO examination routinely for B-TM patients for early detection of cardiac complications in patients with B-TM. The same finding was mentioned in many previous studies***(Faruqi et al.,2015),(Mahmoodi et al.,2019) and (Alipour et al.,2021)*** [14],[15],[16]**.**

Pulmonary hypertension (PH) is one of the common complications in children with thalassemia syndromes . It may play a significant role in the disease mechanism of right ventricular failure. The cause of the widespread pulmonary hypertension in these patients remains unclear[17].

Thalassemia is widely regarded as the most common cause of PAH[18].

Increased incidence of pulmonary hypertension in B-TM patients in our study is found with increased range of age in years with (P =0,054) ,this result is opposite the result detected by ***Mohammed et al.,2020***[19]**.**with (P = 0.77) between age and PH .

while no significant correlation between gender and the incidence of pulmonary hypertension ***(Table 2).***

Also we found no correlation between the level of serum ferritin and the incidence of pulmonary hypertension (P=0.188) , while in the study by ***Mohammed et al.,2020***[19]**.** there was a positive correlation between S. ferritin and PH.

Regarding the relation between pulmonary hypertension and iron chelator intake in Patients included in our study ,we found no correlation between the incidence of pulmonary hypertension and iron chelator intake in these patients with P=0.597 **.**while in the study by ***Vlahos et***

al.,2012[20] incidence and degree of pulmonary hypertension decrease with an improvement of the use of iron chelation therapy.

The patients In this study showed a significant association between pulmonary hypertension and impaired cardiac function (P=0.022) (***Table3)***.This is the result showed in the study by ***Behzad et al.,2015*** in which cardiac function was reduced in thalassemia major patients with PAH.

Many studies have found a link between splenectomy and pulmonary hypertension as a study by ***Hoeper et al.,1999***[21] and ***Crouser et al.,2017***[22]**.**

But in this study we found no correlation between splenectomy and increased incidence of pulmonary hypertension ***(Table 4)*** as the results showed in the studies by ***Rorholt et al.,2017***[23] and **Kimmig and Palevsky,*2016***[24]**.**

Conclusion: In this study ,children with a beta-thalassemia major who were compared with controls, had Significantly high pulmonary artery pressure which is significantly associated with impaired cardiac function.

Acknowledgment

I extend my sincere thanks and gratitude to **Dr. Hanaa**Professor ،**Hassan Mahmoud** of Hematology, Department of Pediatrics, Fayoum University, for her supervision of this work.

I would also like to express my sincere **Sarah** .appreciation and gratitude to Dr **rahim AbuIbE**Pediatrics ،**Nour-l** Professor at the Faculty of Medicine, Fayoum University, for helping me in this work and for spending her time and effort to help meto .finish this work

I also dedicate this work to my dear neonatologist **Dr. Mohammed Essam Ibrahim ,**Egyptian fellowship in neonatology for his continuous encouragement and support.

I would like to thank everyone who helped me during this work, from fellow doctors and nursing, as well as the families of patients who cooperated with me in this work.

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