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Cardiac affection in pediatric patients with β-thalassemia major

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Abstract

Introduction: 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 other complications such as cardiomyopathy and pulmonary hypertension (PH) due to iron overload.

Aim of the study: To detect cardiac affection early in beta-thalassemia major pediatrics.

Subjects and Methods: Echocardiography was done for 50 children with B-thalassemia major in comparison with another 50 children as a healthy control group.

Results: Echocardiography results were correlated with the laboratory data of patients. Significant high pulmonary artery pressure was detected in 38% of patients. The impaired function was significantly associated with PH while was not significantly correlated with serum ferritin.

Conclusion: Children with beta-thalassemia usually complain of high pulmonary artery pressure, which is thought to be associated with impaired cardiac function.

Keywords: Beta thalassemia major; Pulmonary hypertension; Iron overload.

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1. 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]. That 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].

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]. The current study aimed to test the echocardiography outcomes in pediatric patients with B-thalassemia major and correlate results with laboratory data for early detection of cardiac affection in these patients.

2. Subjects and methods

2.1. Subjects

The current case-control study recruited 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. The study was hospital-based and conducted in the Hematology/pediatric and Pediatric Cardiology Outpatient Clinics at Fayoum University Pediatric Hospital, Fayoum, Egypt.

2.2. Inclusion criteria

Children with thalassemia major, Ages ranged between 2-14 years and both genders were recruited.

2.3. Exclusion criteria:

Patients with congenital heart diseases, rheumatic heart diseases, and hemoglobinopathy other than thalassemia were excluded from the study.

2.4. Study design

Medical history

The full medical reports of cases that focused 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

That included general examination, Cardiac examination, Chest examination, and Abdominal examination.

Laboratory investigations

That included complete blood count (CBC) with hemoglobin (Hb) and reticulocyte counts. It also included the estimation of both serum ferritin and serum iron levels.

Echocardiography (ECHO)

A pediatric cardiologist conducted an ECHO study on all of the patients using a Vivid-5 color Doppler ultrasound echocardiography machine (GE Healthcare, Chicago, IL, United States). A complete echocardiographic examination was performed to exclude the presence of any primary cardiac diseases with great

emphasis on left ventricular (LV), right ventricular (RV), and left atrial (LA) dimensions. 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) was performed. The assessment of LA diameter, AO diameter, and LA/Ro ratio was evaluated, as well. Using continuous wave (CW) Doppler, tricuspid regurge (TR) peak signal velocity was assessed and pulmonary artery pressure so on using the simplified Bernoulli equation ($P=4\ (TRmax)^2$).

2.5. 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.

2.6. Statistical Methods

Statistical Package for Social Sciences was used for data handling (version 15.0; SPSS Inc., Chicago, IL, USA). The data were summarized using basic descriptive statistics, such as mean and standard deviation. Simple X^2 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<0.05* was regarded as significant probability values.

3. Results

ECHO showed that 38% of β-thalassemia patients had PH and 6% with impaired cardiac function. Many factors were correlated with pulmonary hypertension with significant correlation including age in years with (*P =0.054*) and impaired cardiac function with (*P=0.022*). In contrast, others had no correlation with PH including serum ferritin with (*P=0.188*), iron chelator intake (*P=0.597*), and splenectomy (*P=0.975*). Serum ferritin level had no significant relation with PH and impaired function. 52% of β-thalassemia patients were males with a ratio of 1.08 between males and females, with age ranged from 2 to 14 with a mean value of 7.4 ± 3.3 SD (Tables 1-2, Figure 1).

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

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

#Independent-t test, ##Chi-squared test, SD=standard deviation.

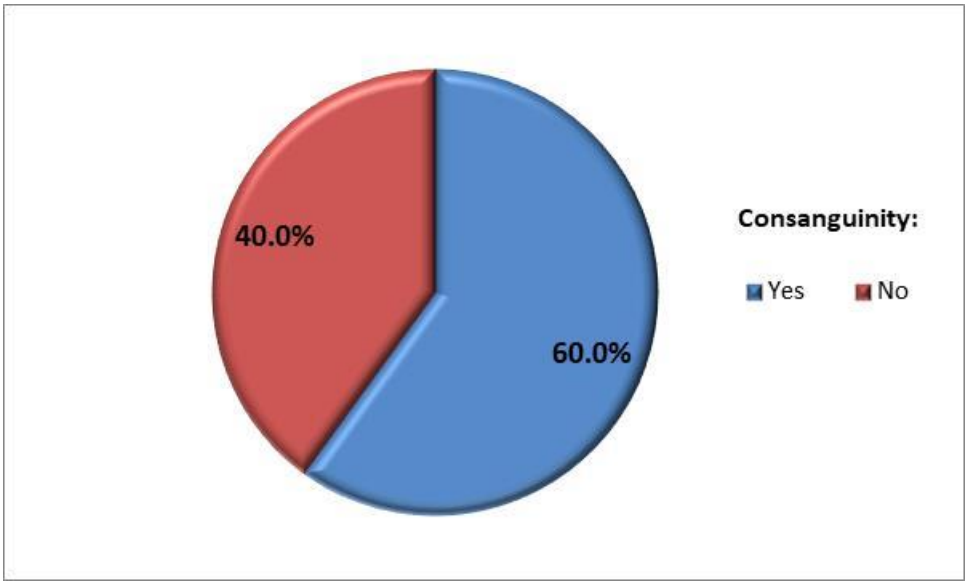

Figure 1: Distribution of B-TM patients according to consanguinity.

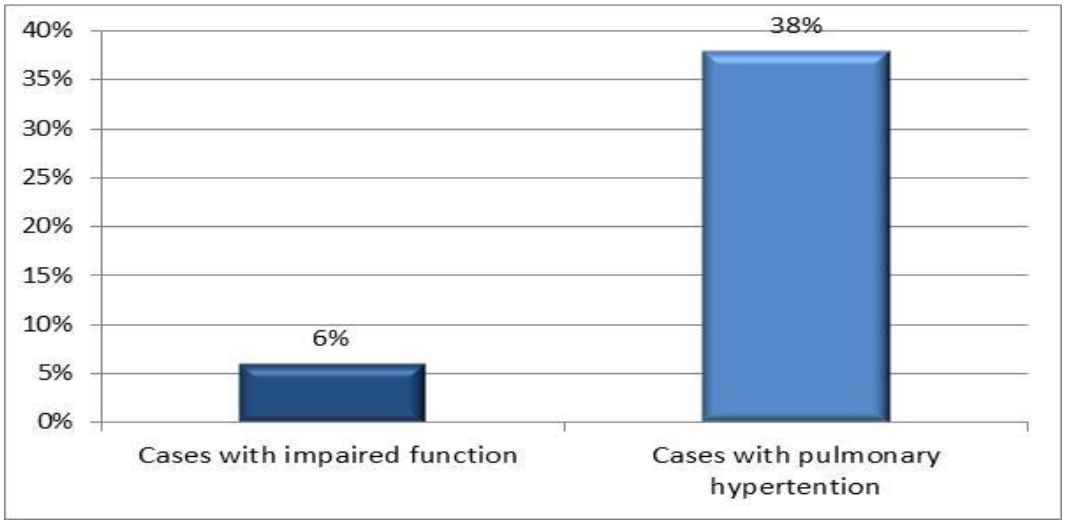

Figure 2: Distribution of β-thalassemia patients according to impaired cardiac function and pulmonary hypertension.

Table 2: Relation between socio-demographics and PH.

		PH		*P-value#*
		Yes	No	
Age (years) Mean ±SD		8.5±3.5	6.7±3	0.054
Sex	Male	9 (47.4%)	17 (54.8%)	0.608
	Female	10 (52.6%)	14 (45.2%)	

According to Table 2, there was 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. Furthermore, Table 3 showed a significant association between PH and impaired cardiac function. Finally, Table 4 didn't reveal any correlation between splenectomy and PH.

Table 3: Relation between impaired function and PH.

		PH		*P-value#*
		Yes	No	
Impaired function	Yes	3 (15.8%)	0 (0%)	0.022*
	No	16 (84.2%)	31 (100%)	

Mann-Whitney U test; *Significant.

Table 4: Relation between splenectomy and PH.

		PH		*P-value#*
		Yes	No	
Splenectomy	Yes	5 (62.5%)	3 (37.5%)	0.975
	No	26 (61.9%)	16 (38.1%)	

4. 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 had a high prevalence of mortality and morbidity, making it the most prevalent hemoglobin disorder in Egypt [9]. In Egypt, the carrier rate ranged 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 β-thalassemia major. In Egypt, the average annual financial cost of managing β-thalassemia is estimated to be $10 million, and this expense is rising. There are 9912 patients with B-thalassemia registered in the main Egyptian centers [10].

In the current study, out of 50 B-thalassemia patients included in our study, 26 were males and 24 were females with a ratio of 1.08 between males and females. So, both genders are affected but with a slightly male predominance. That male predominance was shown in previous studies [11-12]. 60 % of β-thalassemia patients included in this study were of consanguineous marriage and 44 % of patients had positive family history. the results supported the role of inheritance in β-thalassemia patients as shown in the study by Nasreen *et al.* (2010) [13].

In the current study, the Echocardiographic examination of the 50 β-thalassemia patients showed that 38% of cases had PH and 6% of them had impaired cardiac function. only the patients with impaired cardiac function presented with clinical symptoms during the examination as dyspnea and suffered from difficulty to make an ordinary effort, while the majority of cases with cardiac affection had no cardiac symptoms. That agreed with the high importance of both ECG and ECHO examination routinely for early detection of cardiac complications in patients with B-thalassemia. The same finding was mentioned in many previous studies [14-16].

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 PH in these patients remains unclear [17]. Thalassemia is widely regarded as the most common cause of PH [18]. In the current study, the Increased incidence of PH in B-thalassemia patients had an increased range of age in years with (*P=0.054*). That result was in contrast to the results detected by Mohammed *et al.* (2020) with (*P=0.77*) between age and PH [19], while no significant correlation between gender and the incidence of PH. Also, we didn't recognize any 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 them.

Regarding the relation between PH and iron chelator intake in Patients included in our study, we didn't recognize any correlation between the incidence of PH and iron chelator intake in these patients (*P=0.597*). In the study conducted by Vlahos *et al.* (2012), the incidence and degree of PH decreased with an improvement in the use of iron chelation therapy [20].

Furthermore, the current findings showed a significant association between PH and impaired cardiac function (*P=0.022*). That agreed with the findings of

a previous study conducted by Fraidenburg and Machado (2016) in which cardiac function was reduced in thalassemia major patients with PH [21]. Many studies have found a link between splenectomy and pulmonary hypertension [22-23]. However, in the current study, no correlation between splenectomy and increased incidence of PH was detected, which was in contrast to the findings of other previous studies [24-25].

5. Conclusion

In that study, children with β-thalassemia had Significantly high pulmonary artery pressure, which was significantly associated with impaired cardiac function.

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Ethical Approval Statement: The protocol was approved by the local institutional ethics committee of Fayoum University Hospital.

Informed Consent Statement: A detailed informed consent had been signed by the eligible participants (Parents) before recruitment and randomization.

Conflicts of Interest: All authors declare no conflict of interest.

Availability of data and material: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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