Original Article

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Quick Response Code:

Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_12_19

Evaluation of cardiac complications in transfusion-dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT) beta thalassemia patients

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Abstract:

BACKGROUND: Cardiac complications are still the primary cause of mortality and a major cause of morbidity in thalassemia patients.

OBJECTIVES: The aims of this study were to assess the prevalence of cardiac involvement in TDT and NTDT beta thalassemia patients and compare between the different forms and severity in both groups.

MATERIALS AND METHODS: In this prospective study, 70 TDT and 50 NTDT β-thalassemia patients were recruited; their cardiac status was evaluated by transthoracic echocardiography as per the standard recommendations. Patients' cardiac status was evaluated against the causal risk factors.

RESULTS: The mean serum ferritin level was significantly ($P < 0.001$) higher in the TDT patients (4940 ± 3643 ng/mL) compared to the NTDT patients (634 ± 520 ng/mL). The mean hemoglobin was significantly ($P = 0.004$) higher in the TDT group (9.2 ± 0.8 vs. 8.7 ± 1.0 g/dL). The prevalence of dilated cardiomyopathy and left cardiac dysfunction in TDT was 18.6%, whereas pulmonary hypertension (PHT) was found in 30% of NTDT patients.

CONCLUSION: Dilated cardiomyopathy was prevailing in the adult TDT patients, whereas PHT was the main cardiac complication in NTDT patients.

Keywords:

Cardiac complications, echocardiography, β-thalassemia

Introduction

β-thalassemia is an inherited autosomal recessive disorder caused by reduction or absence of the hemoglobin (Hb) β-globin chain synthesis. It presents in one of the three clinical phenotypes: transfusion-dependent thalassemia (TDT) major (TM), nontransfusion-dependent thalassemia (NTDT), and thalassemia minor.[1]

TDT is a subset of thalassemia that requires regular red blood cell (RBC) transfusions for survival. The only curative treatment for TDT is stem cell transplantation, which has limited availability due to a lack of donors. Therefore, the main stay of long-term management is RBC transfusion.[2] NTDT includes thalassemia patients who do not require frequent blood transfusions for survival, but they may still require occasional or more frequent RBC transfusion therapy in certain circumstances including but not limited to significant infection, pregnancy, periods of rapid growth, or surgery.[3]

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Submission: 19-07-2019
Accepted: 15-09-2019
Published: 15-04-2020

How to cite this article: Nameq MS, Shamoon RP, Saka MH. Evaluation of cardiac complications in transfusion-dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT) beta thalassemia patients. Iraqi J Hematol 2020;9:11-6.

Recently, with the improvement in the overall care provided to thalassemia patients and resultant increase in their survival rates, complications related to iron overload, including cardiac complications, have been increasing.[4] Reducing iron load is associated with a reduced incidence of heart failure (HF) and increased survival. Cardiac function may stay normal for many years; however, when symptoms of heart appear, death usually occurs within a relatively short period of time.[5,6]

In TDT, the most leading cause of death is iron overload cardiomyopathy, which causes an end-stage dilated cardiomyopathy and left HF.[7] In NTDT, pulmonary hypertension (PHT) with continuous increase in tricuspid regurgitation and right side cardiac dysfunction is the main manifestation.[8] The pathophysiology of cardiac complications in TDT and NTDT is different where iron overload plays a significant role in the pathophysiology of HF in the former, whereas hypoxia and chronic hemolysis remain the main causative factors of heart disease in later.[9]

Because cardiac complications are considered as the primary cause of mortality and a major cause of morbidity in all thalassemia patients, we deemed necessary to estimate the prevalence, assess the magnitude, and compare the type and severity of cardiac complications in both TDT and NTDT patient groups.

Materials and Methods

This cross-sectional comparative study was conducted on 120 β-thalassemia patients. In this cohort, we included 70 TDT and 50 NTDT. β-thalassemia patients who were age and gender matched. The patients were conveniently enrolled from an Erbil thalassemia day care center between August 2018 and March 2019. The clinical diagnosis and genetic confirmation of the NTDT patients has been done in a previous study.[10]

Demographic data, including age at first transfusion, frequency of transfusion, and history of splenectomy, were retrieved from patients' files. History and clinical examination regarding the presence of any signs and symptoms of heart disease were estimated including shortness of breath, fatigue, palpitation, chest pain, syncope, ankle swelling, elevated jugular venous pressure (JVP), pulmonary crackles, and peripheral edema.

Venous blood was collected into ethylenediaminetetraacetic acid and gel tubes; full blood count was performed using an automated analyzer. Serum ferritin levels were measured using an automated immune analyzer, Cobas E411, Roche, Germany.

All patients had transthoracic echocardiography by Vivid T8 (GE) echo systems. A special transducer was used for pediatrics. Complete M-mode, two-dimensional, and Doppler echocardiography was performed at rest. All echo-Doppler studies were carried out by one expert cardiologist.

Echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging for adults and pediatrics.[11-13] Echo parameters were analyzed according to the aforementioned guidelines; for pediatric cases, the parameters were analyzed against the body surface area.

The following echo parameters were measured: left ventricular ejection fraction; left ventricular end-diastolic and end-systolic dimension; right ventricular dimension and its wall thickness; TAPSE (tricuspid annular plane systolic excursion); left atrial dimension, area and volume; right atrial area and volume; E/A ratio and tricuspid regurgitation jet velocity. Pulmonary artery systolic pressure was estimated by measuring the tricuspid regurgitation jet velocity (TRV), which is the retrograde blood flow across the tricuspid valve during systole. TRV estimates the RV systolic pressure and correlates it with pulmonary artery pressure. The TRV cutoff point was set at 2.5 m/s.

At the end, after taking full history and examination to all thalassemia patients regarding any signs and symptoms of HF and after doing echocardiography to them and depending on measurement of the LVEF as the main terminology used to describe HF, as mentioned by the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF,[14] a final conclusive remark about the patient's cardiac status was provided by the cardiologist: "normal cardiac state," "mildly affected" when there is mildly dilated cardiomyopathy with preserved cardiac function, and "markedly affected" when there is HF.

Ethical considerations

The study had been approved by the Ethics Committee of Hawler Medical University, and informed consent was taken from the all patients or guardians.

Statistical analysis

Statistical analysis was performed using the SPSS 22 statistical software package. Continuous variables were expressed as mean ± standard deviation. $P < 0.05$ was considered statistically significant. Student's *t*-test and Chi-square test were used to compare variables between TM and thalassemia intermedia patient groups.

Results

In this study, 120 patients with β-thalassemia, 70 with TDT and 50 with NTDT, were studied. The two groups were age and gender matched. Children and adolescents constituted 36.6% (44/120), of whom 24 cases were TDT and 20 were NTDT. The age range for TDT patients was 7–46 years and for NTDT was 9–50 years. The demographic and clinical data of the two groups are summarized in Table 1.

There was a statistically significant difference in the age at diagnosis, age at first transfusion, and serum ferritin level in the TDT and NTDT groups. The mean pretransfusion Hb of the TDT patients was higher (9.2 g/dL) than the random Hb level of the NTDT group (8.7 g/dL).

In the pediatric age group, very small proportion of patients showed abnormal echocardiographic parameters with no difference between TDT and NTDT patients [Table 2]. In adults, impaired echo parameters were encountered at higher rates; the LV parameters were remarkably more aberrant in the TDT patients as illustrated in Table 3. In the NTDT group, PHT was encountered at a significantly higher rate comparing to the TDT patients.

The effect of risk factors of gender, age, Hb, serum ferritin level, and splenectomy on the overall cardiac state in the TDT and NTDT patients are illustrated in Tables 4 and 5, respectively. The prevalence of remarkable cardiac impairment among the TDT group was 18.6% (13 patients), whereas only 2 (4%) patients of the NTDT group had cardiac impairment. Patient's age and splenectomy showed significant effect on the overall cardiac status in both TDT and NTDT groups.

Table 1: Demographic and clinical data of transfusion-dependent thalassemia and NTDT patients

	TDT (%)	NTDT (%)	*P*
Children and adolescents (0-16 years)	24 (34.3)	20 (40)	0.522
Adults (≥17 years)	46 (65.7)	30 (60)	
Male	34 (48.6)	23 (46)	0.781
Female	36 (51.4)	27 (54)	
Age, mean±SD	21±8.81	23.9±11.28	0.118
Age at diagnosis, mean±SD	1.2±0.88	11.7±9.99	<0.001
Age at first transfusion, mean±SD	1.25±0.89	12±9.8	<0.001
Serum ferritin (ng/mL), mean±SD	4940±3643	634.7±520	<0.001
Hb (g/dL)*, mean±SD	9.2±0.89	8.7±1.03	0.004
Splenectomy	36 (51.4)	14 (28)	0.01

*Pretransfusion level in TDT; random level for NTDT patients. SD=Standard deviation, TDT=Transfusion-dependent thalassemia, NTDT=Non-TDT, Hb=Hemoglobin

Table 2: Impaired echo parameters in the pediatric TDT and NTDT patients

Echo parameters	TDT (24 cases; 34.3%)	NTDT (20 cases; 40%)	*P*
LVEF	2 (8.3%)	0	0.493
LVEDD	2 (8.3%)	0	0.493
LVESD	2 (8.3%)	0	0.493
RV	3 (12.5%)	0	0.239
RV wall thickness	4 (16.7%)	1 (5%)	0.356
TAPSE	8 (33%)	0	0.004
LA	2 (8.3%)	0	0.493
LAA	3 (12.5%)	0	0.239
LA volume	3 (12.5%)	0	0.239
RAA	3 (12.5%)	0	0.239
RA volume	3 (12.5%)	0	0.239
E/A ratio			
Decreased	0	0	0.239
Increased	3 (12.5%)	0	
TRV	0	0	-

LVEF=left ventricular ejection fraction, LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, RV=right ventricle, TAPSE=tricuspid annular plane systolic excursion, LA=left atrium, LAA=left atrial area, RAA=right atrial area, E/A ratio=peak E (early mitral valve flow velocity)/peak A (late mitral flow velocity), TRV=tricuspid regurgitation jet velocity

Discussion

Despite the advances in therapeutic management of thalassemia and resulting substantial improvement of patients' survival, heart disease always represented and still remains the primary reason of mortality and a major cause of morbidity in all thalassemic patients. Little is known about the prevalence and extent of cardiac involvement in our registered thalassemia patients, mainly among the NTDT group. In this study, we assessed the cardiac status of a cohort of 70 TDT and 50 NTDT patients using transthoracic echocardiography. Both groups were matched for age and gender.

In the current cohort, the mean pretransfusion Hb of the TDT patients was significantly higher than the mean Hb of the NTDT patients. Within the latter group, 14 (28%) patients never received blood and 22 (44%) others occasionally received blood transfusion (once every ≥2 years). In reverse, patients of the former group are on regular transfusion and chelation therapy. Similar results had been reported by Ferrara *et al*. in 2004;[15] however, Karimi *et al*. from Iran reported higher Hb levels among NTDT patients who were treated by hydroxyurea.[16]

The β-thalassemia cardiac disease is mainly characterized by two distinct phenotypes: a dilated phenotype with LV dilatation and impaired contractility, which is mainly seen in the TDT, and a restrictive phenotype with restrictive LV filling and PHT, which is mostly encountered in patients with NTDT.[17]

It is well known that cardiac complications in thalassemia are related mainly to two factors, the iron overload resulted from repeated transfusions in the TDT and administration of effective and regular chelation

therapy.[18] Based on this, and comparable to the results of previous studies which reported minimum cardiac complications in the pediatric thalassemia patients, echocardiographic assessment of our children and adolescent patients revealed that majority had normal echo. In adults, there was increased end-diastolic volume, resting tachycardia, and high cardiac output in both TDT and NTDT patients because of the cardiovascular adaptation to chronic anemia resulting in increased left and right cardiac chambers' dimensions and volumes. Similar findings were reported by other articles.[17,19] LV dysfunction was found to be related to long exposure to iron; our results showed a significant relationship between increasing serum ferritin and LV dysfunction. Similar correlations have been repeatedly reported.[6,20-23] The rate of cardiac complications among the TDT patients was significantly higher some 30 years ago comparing to the recent studies including the current study;[5,20,24] this is probably related to the improved medical care, provision of effective iron chelation, and early identification and treatment of patients at risk for cardiac complications.[25]

Table 3: Impaired echo parameters in the adult TDT and NTDT patients

Echo parameters	TDT (46 cases; 65.7%)	NTDT (30 cases; 60%)	*P*
LVEF	12 (26.1%)	3 (10%)	0.085
LVEDD	13 (28.3%)	3 (10%)	0.056
LVESD	9 (19.6%)	1 (3.3%)	0.078
RV	17 (36.9%)	5 (16.6%)	0.056
RV wall thickness	31 (67.4%)	9 (30%)	0.001
TAPSE	6 (13%)	0	0.07
LA	13 (28.2)	5 (16.6%)	0.245
LAA	14 (30.4%)	8 (26.7%)	0.723
LA volume	13 (28.2%)	13 (43.3%)	0.175
RAA	14 (30.4%)	10 (33.3%)	0.79
RA volume	19 (41.3%)	8 (26.7%)	0.341
E/A ratio			0.321
Decreased	2 (4.3%)	2 (6.7%)	
Increased	9 (19.6%)	2 (6.7%)	
TRV	2 (4.3%)	9 (30%)	0.01

LVEF=left ventricular ejection fraction, LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, RV=right ventricle, TAPSE=tricuspid annular plane systolic excursion, LA=left atrium, LAA=left atrial area, RAA=right atrial area, E/A ratio=peak E (early mitral valve flow velocity)/peak A (late mitral flow velocity), TRV=tricuspid regurgitation jet velocity

Increased pulmonary vascular resistance leading to PHT and right side heart disease is the principal form of cardiac complication among the NTDT patients. PHT was encountered in 30% and 4.3% of only adults NTDT and TDT patients, respectively; none of the pediatric thalassemia patients had increase in the pulmonary pressure. The rate of occurrence of PHT in NTDT seems to be variable as the disease itself; a wide range of prevalence figures of PHT ranging from 18.5% to 60% have been previously reported.[26-29] This diverse range in the incidence of PHT among the NTDT is possibly multifactorial; patients' characteristics, especially their ages, the level of care services, and chelation therapy, are among the important variables. However, the clinical diversity of NTDT, reflected by the disease's genetic diversity, remains the principal factor which determines disease severity and hence its complications. It is worth to mention here that the use of different methods for measuring and detecting pulmonary arterial pressure with different sensitivity and specificity could also affect the results. Some researchers consider right heart catheterization as the definitive method of determining PHT,[29] but we chose to use echocardiography as it is noninvasive and recommended as a screening tool by other authors.[30]

Table 4: Effect of risk factors on the cardiac status in the transfusion-dependent thalassemia patients

	Normal (39/70; 55.7%) (%)	Mild impairment (18/70; 25.7) (%)	Marked impairment (13/70; 18.6%) (%)	*P*
Gender				
Male	20 (58.8)	9 (26.5)	5 (14.7)	0.718
Female	19 (52.8)	9 (25)	8 (22.2)	
Age (years)				
<10	4 (100)	0	0	<0.001
10-19	27 (87.1)	2 (6.5)	2 (6.5)	
20-29	6 (27.3)	11 (50)	5 (22.7)	
≥30	2 (15.5)	5 (38.4)	6 (46.1)	
Hb (g/dL)				
<9	13 (48.1)	7 (25.9)	7 (25.9)	0.421
≥9	26 (60.5)	11 (25.6)	6 (14)	
Serum Ferritin (ng/mL)				
<1000	2 (40)	3 (60)	0	0.024
1000-3000	18 (72)	6 (24)	1 (4)	
>3000	19 (47.5)	9 (22.5)	12 (30)	
Splenectomy				
No	29 (85.3)	4 (11.8)	1 (2.9)	<0.001
Yes	10 (27.8)	14 (38.9)	12 (33.3)	

Hb=Hemoglobin

Table 5: Effect of risk factors on the cardiac status in the NTDT patients

Variable	Normal (32/50; 64%) (%)	Mild impairment (16/50; 32%) (%)	Marked impairment (2/50; 4%) (%)	*P*
Gender				
Male	12 (52.2)	10 (43.5)	1 (4.3)	0.203
Female	20 (74.1)	6 (22.2)	1 (3.7)	
Age group (years)				
<10	2 (100)	0	0	<0.001
10-19	17 (94.4)	1 (5.6)	0	
20-29	9 (69.2)	4 (30.8)	0	
≥30	4 (23.5)	11 (64.7)	2 (11.8)	
Hb (g/dL)				
<9	18 (64.3)	9 (32.1)	1 (3.6)	1.000
≥9	14 (63.6)	7 (31.8)	1 (4.5)	
Serum ferritin (ng/mL)				
<500	21 (75)	7 (25)	0	0.182
500-1000	6 (45.5)	4 (36.4)	1 (9.1)	
>1000	5 (45.5)	5 (45.5)	1 (9.1)	
Splenectomy				
No	27 (75)	8 (22.2)	1 (2.8)	0.016
Yes	5 (35.7)	8 (57.1)	1 (7.1)	

Hb=Hemoglobin

In the current cohort, depending on the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF,[14] cardiac dysfunction was encountered in 13 (18.6%) TDT and 2 (4%) NTDT patients. There was mild echocardiographic aberrations in the form of dilated one or more than one chamber, but with otherwise normal cardiac function encountered in 18 (25.7%) and 16 (32%) TDT and NTDT patients, respectively [Tables 4 and 5]. When we analyzed the possible risk factors of cardiac complications, we found that increasing age, higher serum ferritin levels, and splenectomy are significantly associated impaired cardiac status in the TDT group. However, ferritin level did not show significant association in the NTDT group. Cardiac dysfunction mainly occurs after the age of 10 years, and advancing age means more iron absorption and more iron deposition; however, it may occasionally occur before that age, especially when access to chelation is limited.[18,31] In both groups, patients' gender and Hb level were of no effect on the cardiac status. Splenectomy plays a significant role, mainly in the NTDT, in removing hematologic debris (phosphatidylserine-positive platelets, platelet fragments, and red cell fragments) from the cardiovascular system and suppresses intravascular hemolysis. Therefore, splenectomy is a strong risk factor for intravascular thrombosis and PHT.[32,33]

Conclusion

Cardiac complications in the pediatric TDT and NTDT were of little significance. The LV dimensions and function parameters were found defected more among the TDT patients (28%); however, impaired cardiac function was noted in 18.6% of them. PHT, on the other hand, was seen more in the NTDT group, of whom only 2 (4%) patients had impaired cardiac function. Age and splenectomy found to have significant correlation with impaired cardiac function in both groups. Echocardiography remains a useful screening tool for assessing cardiac siderosis and monitoring cardiac function in thalassemia patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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