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Assessment of Cardiac Functions and Arrhythmia in Children with Beta-Thalassemia Major and Beta-Thalassemia Intermedia

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Abstract

BACKGROUND: Heart disease is a major complication in thalassemic patients. Heart injuries in iron overload cases include arrhythmia, pulmonary hypertension, systolic/diastolic dysfunction, and heart failure.

AIM: This study aimed to assess cardiac functions and arrhythmia in children with β-thalassemia major (TM) and β-thalassemia intermedia (TI) and its relation to cardiac iron overload.

METHODS: Thirty β-TM patients and 30 β-TI patients were evaluated using echocardiography and 24-h ambulatory electrocardiogram monitoring (Holter). Among these patients, 15 β-TM and 15 β-TI patients were evaluated using cardiac magnetic resonance imaging T2* by single breath-hold multi-echo technique.

RESULTS: Arrhythmia was detected significantly more in β-TM patients than β-TI ($p = 0.049$). Nine (30%) β-TM and five (16.6%) β-TI patients had Sinus tachycardia. Two (6.7%) β-TM patients compared to one (3.33%) β-TI patient had supraventricular tachycardia runs. Three (10%) β-TM and one (3.33%) β-TI patient had extreme sinus tachycardia. Two (3.3%) β-TI patients had sinus bradycardia, while two (3.3%) β-TM patients had incomplete Right bundle branch block. Regarding echo parameters: Isovolumic relaxation time (IVRT), Left ventricle myocardial performance index (MPI LV), Right ventricle myocardial performance index (MPI RV) and end systolic pulmonary artery pressure, were significantly higher in β-TM than TI group ($p < 0.05$). Fractional shortening, Ejection fraction were significantly lower in β-TM than TI group ($p < 0.001$). A statistically significant negative correlation was found between cardiac T2* and each of (IVRT, MPI LV, MPI RV) ($p < 0.05$).

CONCLUSION: Arrhythmias are more common in the β-TM group. Systolic, diastolic dysfunction and high pulmonary pressure are more prevalent in TM than in TI. Global myocardial performance is more impaired in TM than in TI patients. Iron overload has a deleterious effect on cardiac function.

Introduction

Thalassemia is a group of heterogeneous diseases inherited in autosomal recessive manner, characterized by microcytic, hypochromic anemia due to disrupted synthesis of hemoglobin chains [1]. Two classifications of thalassemia are the alpha (α) and beta (β) thalassemias, containing deficits in (α) and (β) globin production, respectively. Regular blood transfusion and adequate iron chelation therapy are two main factors for the treatment of β-thalassemia patients [2].

Regular blood transfusions, lack of iron excretion and increased intestinal iron absorption, all lead to an excess accumulation of iron in the body of thalassemic patients [3]. The consequent iron accumulation in the liver, endocrine organs, and heart is a major cause of morbidity and mortality in patients with thalassemia [4].

Cardiac complications represent a major health concern of β thalassemia patients whether major or intermedia [5]. Cardiac disease can manifest as arrythmias, systolic/diastolic dysfunction, cardiomyopathy, pulmonary hypertension, heart failure, pericardial effusion, and myocarditis or pericarditis [6]. Iron deposition, with immunogenic and inflammatory factors are involved in the pathophysiology of cardiac dysfunction in these patients [7], [8]. Holter electrocardiogram is used to detect and determine the kind of arrhythmia [8], [9].

Cardiac magnetic resonance imaging (CMRI) T2* is the best method for assessing myocardial iron and the most useful technique to predict the risk for cardiac dysfunction in thalassemic patients, in addition to its ability to correlate the cardiac iron status to electrocardiographic results [8], [10].

This study was performed to detect the presence of arrhythmia and impairment in cardiac functions in Egyptian β-Thalassemia patients and its correlation to cardiac iron overload.

Methods

This cross-sectional study was conducted on 60 thalassemia patients (30 patients with β-thalassemia major (TM) and 30 patients with β-thalassemia intermedia (TI)), aged 10-18 years old, with no congenital or valvular heart disease, attending regularly at the Pediatric Hematology Clinic, New Cairo Children Hospital, Cairo University over a period of 12 months. The diagnosis of β-TM and β-TI was based on conventional clinical and hematological criteria (complete blood count, hemoglobin electrophoresis and/or high-performance liquid chromatography).

All patients were subjected to the full history, stressing on duration of illness (DOI), transfusion history and chelation therapy used. Full medical examination was done.

Laboratory investigations, including complete blood picture, ALT, AST, blood urea, serum creatinine, and serum ferritin were obtained. Enzyme-linked fluorescent assay method was used to check serum ferritin.

Ethical approval

The study was approved by the Ethical Committee of Faculty of Medicine, Cairo University (ethical clearance number, I-131016). A written consent was obtained from all studied patients.

24-h Holter

All patients were evaluated using 24-h holter. A vision (Schiller MT-101) holter was used in this study. After recording data from patients, using a PC card recorder, the data is copied to the computer. The vision TM Holter system provides a comprehensive and detailed report of the patient's ambulatory cardiac procedure. Sorting the individual QRS complexes into forms based on their features, was done using feature extraction technique. These features include QRS morphology, QRS width, QRS absolute area, QRS offset, QRS peak to peak amplitude, and prematurity.

The forms of QRS complexes are classified into one of the following categories: normal (n), ventricular (v), paced (p) or artifact (x). Identification of supraventricular and ventricular arrhythmia was done. Rate-dependent arrhythmias, tachycardia and bradycardia, are calculated on the basis of the RR intervals measured in an eight beats sliding window. Prior to printing the report, the classification of all forms and arrhythmia episodes were reviewed and edited when necessary.

Arrhythmias were categorized according to American Heart Association/American College of Cardiology guidelines [11].

Echocardiography

Two dimensional, M-mode, color Doppler, and tissue Doppler echocardiographic examinations were performed for all patients, using GE Vivid S5 echocardiography, using probes 3S, to measure cardiac dimensions (Aortic root (AO), Left atrium (LA), Left ventricular end systolic diameter (LVESD), Left ventricular end diastolic diameter (LVEDD)), systolic functions (ejection fraction, fractional shortening, end systolic pulmonary artery pressure (ESPAP)), diastolic functions (Isovolumic relaxation time (IVRT), MVE/A ratio, E/È) and global myocardial performance (left ventricle myocardial performance index (MPILV), right ventricle myocardial performance index (MPIRV)). Echo measurements were done according to the guidelines for performance of echocardiogram by the American Society of Echocardiography [12].

*Cardiac MRIT2**

Half of the patients (15 patients with β-TM and 15 patients with β-TI) were scheduled for CMRIT2* in Radiology department, using a Philips Achiva, Netherland (1.5 Tesla) superconducting magnet with a Torso XL coil. Scans were done parallel to the cardiac cycle by the ECG gating. At mid ventricular part, half distance between the base and the apex of the left ventricle with TR 20ms and multiple TEs (2.4, 4.6, 6.8 and 9.1), a single 10 mm-thick short axis was taken. Flip angle 30 and FOV 320 mm. A region of interest (ROI) was manually drawn encompassing the full thickness of the inter-ventricular septum. The average signal intensity within the ROI was calculated for each image with incremental echo times [13], [14].

Results of MIC (myocardial iron concentration) and cardiac T2* were categorized as follows: normal cardiac iron (MIC < 1.16 mg/g, T2* > 20 ms), light iron overload (MIC = 1.16- 1.65 mg/g, T2* = 15–20 ms), moderate iron overload (MIC = 1.65- 2.71 mg/g, T2* = 10-15 ms), severe cardiac iron overload (MIC> 2.71mg/g, T2*<10 ms) [15].

Statistical analysis

SPSS version 25 was used to code and enter the data. Means and standard deviations or medians and ranges were used to present numeric data. Categorical data was summarized as numbers and percentages. Unpaired *t*-test in normally distributed quantitative variables was used in comparing groups, while non-parametric Kruskal-Wallis and Mann–Whitney tests were used for non-normally distributed quantitative variables. Chi square ($\chi 2$) test was used to compare categorical data, if the expected frequency is less than 5, exact test was performed instead. Spearman correlation coefficient was performed to correlate between quantitative variables. P-values

<0.05 were considered as statistically significant and p ≤ 0.01 was considered as statistically highly significant.

Results

Thirty two patients (53.3%) were males while 28 patients (46.7%) were females. The mean age in TM group was 14.57 (± 2.10) years and in TI group was 13.85 (±2.2) years. Thirty seven of all studied patients (61.7%) were splenectomized (26 β-TM and 11 β-TI). All our patients (TM **and** TI) (100%) were on iron chelating agents.

The mean values of serum ferritin in TM and TI were 2481.70 (± 1899.46) and 830.12 (±852.17) respectively. Twenty two out of 30 patients (73.3%) had normal cardiac T2* while 5 TM patients (33.3%) had light cardiac iron deposition compared to only one TI patient (6.7%) Figure 1. Two TM patients had severe cardiac iron deposition (13.3%).

The study revealed that 25 (41.6%) out of 60 patients had arrhythmias, with a statistically significant increase in number of β-TM patients who had arrhythmia in comparison to β-TI (p = 0.049). The distribution of arrhythmias detected in our patients is shown in Table 1.

Echocardiographic parameters of the studied patients (β-TM and β-TI) were compared together and illustrated in Table 2. Both FS and EF were significantly lower in β-TM than TI group (p < 0.001) indicating impaired systolic function in β-TM than TI patients. IVRT, was significantly higher in β-TM than β-TI group denoting impaired diastolic function in β-TM than TI patients (p < 0.001). MPI LV and MPI RV were significantly higher in β-TM than β-TI group (p = 0.029 and 0.001 respectively), indicating impaired global myocardial performance (systolic and diastolic function) in β-TM than β-TI patients.

A statistically significant (-ve) correlation was detected between FS and each of (age, DOI, number of blood transfusion) (r= –0.292, –0.473, –0.563 respectively) (p = 0.023, < 0.001, < 0.001respectively). A statistically significant (-ve) correlation was detected between EF and each of (age, DOI, number of blood transfusion) (r =–0.323, –0.472, –0.522 respectively) (p = 0.012, < 0.001, < 0.001 respectively).

Duration of illness showed a statistically significant (+ve) correlation with (IVRT) (r = 0.350) (p =0.006). A statistically significant (+ve) correlation was found between Platelet count and (ESPAP) (r = 0.305) (p = 0.018).

Serum ferritin showed (–ve) correlation with both FS and EF (r = **–**0.565, **–**0.584 respectively) (p ≤ 0.001, < 0.001 respectively). A statistically significant (+ve) correlation was observed between serum ferritin and each of (IVRT, MPILV) (r = 0.364, 0.408 respectively) (p = 0.004, 0.002 respectively).

Table 1: Comparison between studied groups as regards distribution of Holter findings

Parameters	Count (%)		p
	TM (n = 30)	TI (n = 30)	
Normal holter			
+	14 (46.6)	21 (70.0)	0.049
–	16 (53.3)	9 (30.0)	
Sinus tachycardia			
+	9 (30)	5 (16.6)	0.052
–	21 (70)	25 (83.3)	
Sinus bradycardia			
+	0 (0.0)	2 (6.7)	0.492
–	30 (100.0)	28 (93.3)	
Extreme sinus tachycardia			
+	3 (10)	1 (3.33)	0.166
–	27 (90)	29 (96.6)	
SVT runs			
+	2 (6.7)	1 (3.33)	0.103
–	28 (93.3)	29 (96.6)	
Incomplete Rt BBB			
+	2 (6.7)	0 (0.0)	0.492
–	28 (93.3)	30 (100.0)	

χ^2: Chi-square test. SVT: Supraventricular tachycardia, Rt BBB: Right bundle branch block, TM: β-thalassemia major, TI: β-thalassemia intermedia. +: patients positive to such a parameter; -: patients not having such a parameter

Cardiac T2* showed a statistically significant negative correlation with each of (IVRT, MPI LV, MPI RV) (r = **–**0.542, **–**0.676, **–**0.529 respectively) (p = 0.001, 0.001, 0.017 respectively).

Table 2: Comparison between studied patients as regards echo parameters

Parameters	TM (n = 30)		TI (n = 30)		p
	Mean ± SD	Median/(range)	Mean ± SD	Median/(range)	
LA	2.43 ± 0.26	2.40/(2–3)	2.44 ± 0.28	2.50/(2–3)	0.811
AO (cm)	2.03 ± 0.30	2.00/(1.4–2.8)	1.90 ± 0.27	1.95/(1.4–2.3)	0.085
LVEDD (mm)	4.26 ± 0.24	4.30/(3.6–4.8)	4.34 ± 0.25	4.40/(3.8–4.7)	0.212
LVESD (mm)	2.83 ± 0.21	2.90/(2.3–3.1)	2.49 ± 0.29	2.60/(2–3)	< 0.001
IVRT (m/s)	85.70 ± 19.13	84.00/(34–122)	66.90 ± 20.2	67.00/(33–104)	< 0.001
MVE/A ratio	1.68 ± 0.30	1.60/(1.2–2.4)	1.64 ± 0.37	1.50/(1.2–2.5)	0.648
E/È	6.43 ± 2.56	5.95/(2.6–10.6)	5.83 ± 1.7	5.60/(3.4–10.2)	0.440
MPI LV	0.65 ± 0.84	0.30/(0.08–2.80)	0.23 ± 0.15	0.23/(0.03–0.74)	0.029
MPI RV	0.42 ± 0.48	0.29/(0.08–1.8)	0.17 ± 0.1	0.13/(0–0.4)	0.001
ESPAP (mmHg)	34.40 ± 4.46	33.50/(30–44)	31.67 ± 4.7	31.50/(22–37)	0.026
FS (%)	33.40 ± 5.10	33.00/(26–46)	42.30 ± 6.8	43.50/(32–53)	<0.001
EF (%)	65.80 ± 9.35	65.00/(52–89)	80.73 ± 12.3	84.00/(50–95)	<0.001

Mann–Whitney test. LA: Left atrium, AO: Aortic root, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, IVRT: Isovolumic relaxation time, E/A: E/A ratio, E: E-wave, A: A-wave, MPI: Myocardial performance index, MPI LV: MPI left ventricle, MPI RV: MPI right ventricle, ESPAP: End systolic pulmonary artery pressure, Fs (%): Fractional shortening, Ef (%): Ejection fraction, TM: β-thalassemia major, TI: β-thalassemia intermedia, SD: Standard deviation.

No significant correlation was detected between cardiac T2* and other echo parameters (LVEDD, LVESD, MVE/A, E/E`, ESPAP, FS, EF) (p < 0.05).

No statistically significant relation was detected in both groups between cardiac T2* and Holter findings (Sinus tachycardia, Extreme sinus tachycardia, supraventricular tachycardia (SVT) Runs) (p > 0.05).

A statistically significant association was revealed between SVT runs and serum ferritin (p = 0.030), where patients with SVT runs had higher mean values of serum ferritin than patients without arrhythmia.

No statistically significant relation was detected in both groups between different echocardiographic findings (LVEDD, LVESD, IVRT, MVE/A, E/E`, MPILV, MPIRV, ESPAP, FS, EF) and Holter findings (p > 0.05).

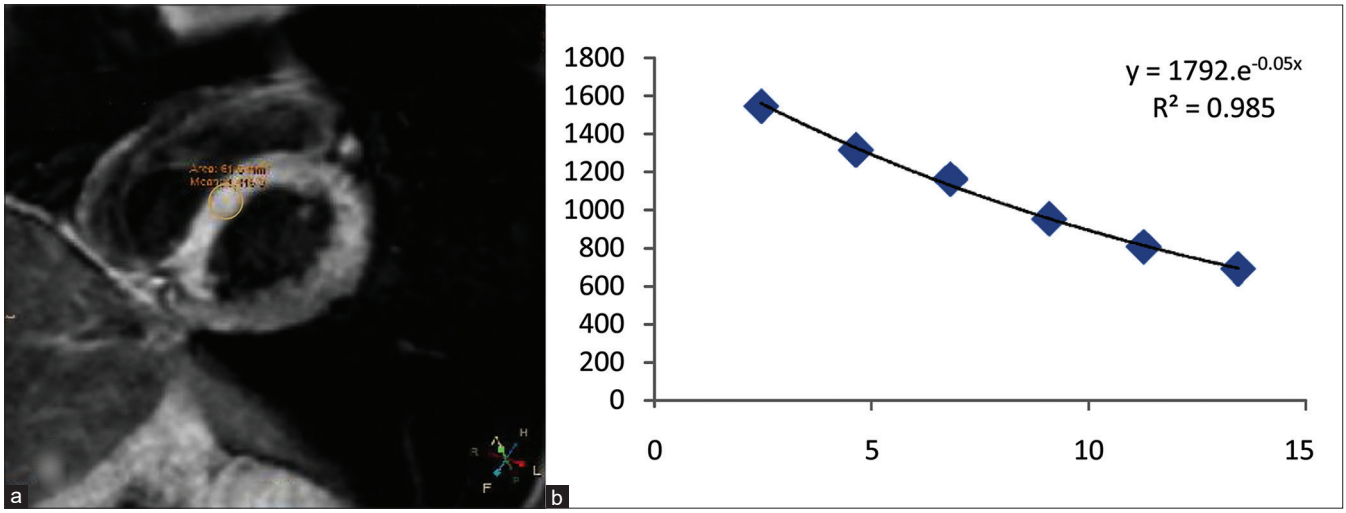

Figure 1: Cardiac MRIT2 of a 16 years old thalassemia intermedia patient with light cardiac iron overload, calculated cardiac T2* equals 18.6 ms and MIC equals 1.27 mg/g (light cardiac iron overload). (a) A region of interest (ROI) was manually drawn encompassing the full thickness of the inter-ventricular septum excluding the blood pool. The average signal intensity within the ROI was calculated with incremental echo times. (b) Calculated cardiac T2* from short-axis images at 6 increasing TEs, with fitting of mono exponential decay curve (Vertical access represents MRI signal intensity, while horizontal access representing echo time by ms)*

Discussion

Different types of arrhythmia were observed in 41.6% of the studied patients most commonly were sinus tachycardia, extreme sinus tachycardia, SVT runs, sinus bradycrdia and incomplete Rt BBB. Multiple studies showed different types of arrhythmia in patients with thalassemia [5], [16]. Amoozgar *et al*., [5] reported, premature atrial contractions (PAC), premature ventricular contractions (PVCs), atrial fibrillation and SVT to be the most frequently arrhythmia detected in thalassmic patients. In another study by Koonrungsesomboon *et al*., [16] in addition to atrial fibrillation and SVT, they reported heart block, ventricular tachycardia, and atrial flutter.

TM patients had significantly more abnormal cardiac rhythm than TI patients, a result which was also reported by Amoozgar *et al*., [5]. This could be attributed to iron cardiotoxicity, chronically elevated cardiac output secondary to anemia, as well as increased cardiac afterload [8]. Among our patients although arrhythmias were more common in TM than TI, both had almost the same rhythm abnormality.

Serum ferritin showed statistically significant relation with SVT where patients with SVT had higher mean values of serum ferritin than patients without arrhythmia. This agreed with Mehmood *et al*., [17] who mentioned that, serum ferritin analysis and electrocardiographic study of TM patients have pointed toward the direct relationship between serum ferritin levels and abnormalities observed in electrocardiogram of these patients. This could be explained as, once labile iron is increased in the myocyte, it increases myocyte oxidative stress. Calcium, sodium, and potassium ion channels are disrupted causing conduction disturbances and arrhythmias [18].

No statistically significant relation was detected between CMRIT2* results and occurrence of arrhythmia detected by Holter. Our results differ from what was reported and concluded by Kirk *et al*., [14] that CMRIT2* identifies patients at high risk of arrhythmia from myocardial siderosis, where he found that a significantly increased risk of arrhythmia associated with cardiac T2* values <20 ms.

Patients with TM had significantly increased (MPILV and MPIRV) than patients with TI. This raised MPI in TM patients was detected by Noori *et al*., [19] as well. The increase in MPI might be attributed to very early myocardial dysfunction not only related to myocardial iron deposition; but also due to the persistence of previous iron related damage on longitudinal fibres [20].

Also IVRT (diastolic performance index), was significantly higher in β-TM than β-TI group. Presence of increased IVRT is a strong and accurate variable in early stages of diastolic dysfunction [21].

Patients with TM had a significant lower values of (FS, EF) than TI patients. Our results are comparable to the results of many studies as Aessopos *et al*., [22] and Noori *et al*., [19].

When ESPAP was measured, it was significantly higher in TM than TI patients. Our results came in concordance with what was previously reported by Fraidenburg and Machado [23] that high pulmonary pressure incidence was more in TM patients than TI patients. This elevated right ventricular systolic pressure in β-TM was related to splenectomy, severity of hemolysis and iron overload [20].

Regarding the negative correlation between serum ferritin and each of (FS, EF), and the positive one between serum ferritin and each of (IVRT, MPI LV), our results agreed with Panda and Sharma [24]. The relation between elevation of serum ferritin and

each of (global myocardial performance impairment, systolic and diastolic dysfunction), could be attributed to labile cellular iron (LCI) which leads to formation of free radicals, resulting in cellular injury. In the heart, this causes impaired mitochondrial respiratory chain function and reduced cardiac muscular contractility [25]. Parenchymal injury secondary to myocardial iron deposition is the most important pathological mechanism in the development of cardiovascular diseases [1].

The significant (-ve) correlation found between cardiac T2* and each of (IVRT, MPILV, MPIRV) among the studied patients came in accordance with the results of Barzin *et al*., [26] and Djer *et al*., [27]. This was against what was detected by Leonardi *et al*., [28] who did not find a correlation between myocardial T2* and diastolic function parameters.

Conclusion

Arrhythmias (sinus tachycardia, extreme sinus tachycardia, SVT runs, and incomplete Rt BBB) are more common in β-TM group than in TI. Systolic and diastolic dysfunction as well as high pulmonary pressure is more common in TM than in TI. Global myocardial performance is more impaired in TM than in TI patients. A significant negative correlation was found between T2* and each of (IVRT, MPI LV, and MPI RV), confirming the deleterious effect of cardiac iron overload on both systolic and diastolic heart function.

Limitations

Differentiation between TM and TI was based on clinical base, not confirmed by genetic study, for financial constraints.

Half of the studied patients were investigated by CMRIT2* due to financial constraints.

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