The corrected QT interval prolongation in adolescents with cardiac iron overload β-thalassemia major

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ABSTRACT

Background and objectives. Iron-induced cardiomyopathy remains the leading cause of mortality in β-thalassemia major patients. The T2* magnetic resonance imaging (MRI) technique is the gold standard for iron load detection, yet it is expensive and not widely available especially in the developing countries. Some previous studies showed that QTc interval could be used as an early detection of cardiac iron overload. This study aimed to evaluate the diagnostic value of QTc interval as a marker of early detection of cardiac iron overload in adolescent beta thalassemia major patients.

Methods. We prospectively evaluated electrocardiography (ECG) parameter of QTc interval in 50 β-thalassemia major patients aged 10-18 years. All participants had a 12-lead ECG evaluation, echocardiogram and cardiac MRI T2* examination within three months (average 15 days). They were categorized as cardiac iron overload (MRI T2* <20 millisecond) and non-cardiac iron overload (MRI T2* >20 millisecond).

Results. Of the 50 patients, the male to female ratio was 1.08:1 and the mean age was 13.7 ± 2.43 years. All participants showed normal systolic and diastolic function using conventional echocardiography. The mean QTc interval was significantly different between cardiac iron overload group (464.44 ± 20.35 ms) and non-cardiac iron overload group (431.09 ± 32.29) (p= 0.001). Diagnostic study of QTc interval resulted in AUC 0.8 (p= 0.002). Calculated sensitivity and specificity of QTc interval were 0.88 and 0.73 respectively, with cut-off point of 449 ms.

Conclusion. Cardiac iron overload is associated with QTc prolongation in adolescents. QTc interval of 449 ms could be considered as a cut-off point of cardiac iron overload.

Key words: adolescent, β- thalassemia major, cardiac MRI T2*, QTc interval.

Thalassemia is the most prevalent single gene-disorder which has 4.5% prevalence of carrier gene and 300.000-500.000 homozygotes born each year.[1] Regular blood transfusion is inevitable in beta thalassemia major due to its nature of chronic hemolysis and impose the risk of having iron overload.[2] Routine blood transfusion in addition to increase of intestinal iron absorption will lead to iron loading in many organs.[2,3] Iron overload or in combination with immunogenetic factors will lead to the development of cardiomyopathy in beta-thalassemia major.[4-6] Despite the advances in iron chelating agent, iron overload cardiomyopathy remains the most important cause of mortality and morbidity.[7-9] Hence, it is of utmost important to detect iron overload early as adequate agent could reverse the disease process.[10-12]

Echocardiography study is the standard monitoring of cardiac function in thalassemia patients yet systolic and diastolic dysfunction are late signs.[13,14] Rhythm monitoring using 12-lead electrocardiography (ECG) was previously considered nonspecific although recent meta-analysis of case control studies has proven otherwise.[15-17] Cardiac magnetic resonance imaging T2-star (T2*) is currently becoming the gold standard of cardiac iron overload

evaluation and has a good correlation with cardiac iron concentration.[18-20] However, it is quite expensive and not widely available in the developing countries.

The incidence of QT prolongation and sudden cardiac death are increased among thalassemia major patients.[21-30] A previous study revealed that increased iron stores are associated with QT prolongation independent of hemochromatosis genotype and inflammation.[17] Therefore, we evaluated the current literature to evaluate the association of QTc interval prolongation and cardiac iron loading. However, to the best of our knowledge there is no such study done exclusively in the adolescent group. The aim of this study was to determine the use of QTc interval prolongation in adolescent beta-thalassemia major to detect cardiac hemosiderosis assessed by MRI T2*.

Material and Methods

Study population

Fifty adolescent patients, aged 10-18 years (27 males, 23 females) with β-thalassemia major were enrolled in this study during June until November 2017. Inclusion criteria were asymptomatic β-thalassemia major patients with pre-transfusion hemoglobin level above 7 g/dl. Patients with clinical sign and symptoms of heart failure, impaired renal and liver function were excluded. All subjects were receiving regular blood transfusions every 2-3 weeks and chelation therapy, which was started before the age of 5 years. At the time of MRI examination, 32 patients were receiving deferiprone (DFP) chelation therapy, 8 deferasirox (DFX), 4 combination therapy of DFP and DFX, 3 combination therapy of DFP and deferoxamine (DFO), and 3 combination therapy of DFP and DFX.

All subjects were evaluated for 12-lead electrocardiography and echocardiography within 3 months after cardiac MRI T2* examination. The local ethics committee approved the study protocol (decision number 424, dated may 8th, 2017) and written informed consent was obtained from all patients and/or parents.

Ferritin measurement

Ferritin levels were determined by an electrochemiluminescence technique using the Roche e 411 Cobas immunoassay analyzer (Roche Diagnostics). The mean serum ferritin value was derived from the mean obtained at 3-months interval over the previous year.

Cardiac iron concentration

T2* MRI examination was performed by 1.5 Tesla MRI scanner (Siemens Avanto Germany). Myocardial T2* was analyzed using dedicated software (Thalassemia-Tools; Cardiovascular Imaging Solutions, London, United Kingdom) with regions of interest in ventricular septum. Each image was acquired during 11-13 s breath-hold, using a gradient echocardiogram sequence. The repetition time was 200 millisecond, the flip angle used was 20^0, echo times was 1.3-23 ms, the base resolution matrix was 128 pixels, the field of view was 39.7 cm and 19.7 cm, and the sampling bandwidth was 125 kHz. Results of cardiac T2* were categorized as severe (T2* < 10 ms), mild to moderate (10 ms <T2*< 20 ms), and acceptable (T2* >20 ms). All investigators involved in the study were blind of any information regarding patient's medical records.

Echocardiography

Systolic function (fractional shortening and ejection fraction) and diastolic function (ratio of the Early (E) to late (A) ventricular filling velocity) were recorded. Normal left systolic function was defined as ejection fraction between 56%-78% and fraction shortening between 28%-44%; while normal diastolic function was defined as E/A ratio 1.9 ± 0.5.[31] Normal right ventricular systolic function was defined as tricuspid annular plane systolic excursion (TAPSE) > 16 mm.[32]

ECG Measurement

We performed 12-lead ECG examinations on all subjects with speed set at 25 mm/second and gain at 10 mm/mV. The ECG was scanned and interpreted manually blinded to the MRI results. Conduction parameters, including PR, QRS, and QT intervals were measured from the average of three consecutive beats mostly in lead II. The QT interval were measured from the start of QRS complex until the end of T wave. The end of QT interval was selected using tangential method.[26] Correction of QT interval for heart rate was calculated using Bazett's formula (QTc = $QT/\sqrt{RR}$). All interval measurements were presented in milliseconds. ECG was measured prior to cardiac MRI examination.

Statistical analysis

All tests were carried out using SPSS (Statistical Package for Social Sciences) version 23 software (IBM Corp., NY, USA). Sample size was calculated using formula for comparing two independet means. Data are expressed as mean ± standard deviation as indicated. Saphiro-Wilk test was performed for testing normality. Statistically significant differences between two groups of continous variables were determined by using independent t-test or Mann-Whitney test as appropriate. Diagnostic study and cut-off were set using receiver operating curve analysis. A P-value < 0.05 was considered statistically significant.

Results

Subjects comprised of 50 patients (mean age 13.7 ± 2.43 years, 54% [n=27] male, 46% [n=23] female) with transfusion dependent β-thalassemia major. Patient's demographic and baseline characteristics are presented in Table I. There were 41 (82%) patients without evidence of cardiac hemosiderosis (T2* >20 ms), while 9 (18%) had cardiac hemosiderosis, (T2* < 20 ms), of whom 2 had severe cardiac hemosiderosis (T2*<10 ms). Mean ferritin serum levels were increased in patients with cardiac hemosiderosis (5185 ± 2247 ng/ml) compared

Table I. Baseline characteristics of patients.

Characteristics	n=50
Gender n (%)	
Male	27 (54)
Female	23 (46)
Age, mean ± SD, years	13.71 ± 2.43
Age at diagnosis, mean ± SD, months	8.19 ± 8.24
Body weight, mean ± SD, kg	33.07 ± 10.05
Frequency of transfusion/year, mean ± SD, times/years	16 ± 3.7
Pre-transfusion Hb, mean ± SD, g/dl	9 ± 1.32
Chelation	
Monotherapy	
DFP	32 (64%)
DFX	8 (16%)
Combination	
DFP+DFX	4 (8%)
DFP+DFO	3 (6%)
DFO+DFX	3 (6%)

SD: Standard deviation, DFP: deferipron, DFX: desferoxamine, DFO: desferral.

to non-siderosis (4339 ± 2011 ng/ml) but it was statistically not significant (p= 0.32).

Echocardiography examination of all patients revealed no abnormalities either in systolic or diastolic parameters as shown in Table II. Of all assessed ECG parameters, only mean QTc interval showed significant difference between cardiac iron overload (CIO) and no-CIO groups (p= 0.001) (Table III). We could not find other causes of long QTc in subjects with prolonged QTc. Further ROC analysis of QTc interval demonstrated an area under curve (AUC) value of 0.835 (p= 0.02 CI 95% 0.705-0.965) for the presence of cardiac iron (Fig. 1). The optimal cut-off point of diagnosis CIO was selected at 449 ms and yielded a sensitivity of 88.9% and a specificity of 73.1%. Negative predictive value (NPV) and positive predictive value (PPV) for this value were 42.1% and 96.7%, respectively.

Discussion

To our knowledge, this is the first study assessing ECG parameters exclusively done in adolescent

Table II. Echocardiography results.

Echo Results	T2* < 20 (n=9)	T2* > 20 (n=41)	p
Left Ventricle Systolic Function			
LVEF, mean ± SD, %	67.2 ± 6.5	66.03 ± 6.4	0.53[a]
FS, mean ± SD, %	35.7 ± 6.7	35.98 ± 4.99	0.92[a]
Right Ventricle Systolic Function			
TAPSE, mean ± SD, mm	22.64 ± 2.91	23.54 ± 4.05	0.55[b]
Diastolic Function			
E/A, mean ± SD	1.78 ± 0.3	1.7 ± 0.26	0.48[a]

[a] Mann-whitney test [b] independent t-test
LVEF: Left ventricular ejection fraction, SD: Standard deviation
FS: Fractional shortening, TAPSE: Tricuspid annular plane systolic excursion
E/A: Ratio of the early to late ventricular filling velocity, mm: millimeter.

Table III. Difference of ECG parameters between CIO and no-CIO patients.

ECG Parameters (mean ± SD)	T2*<20 (n=9)	T2*>20 (n=41)	p
Heart Rate, (BPM)	95 ± 13	86 ± 18	0.09[a]
PR Interval (ms)	134.25 ± 32.77	147.61 ± 21.02	0.13[b]
QRS duration (ms)	77.75 ± 10.21	78.82 ± 13.32	0.921[b]
QT Interval (ms)	417.8 ± 57	387 ± 38.4	0.052a
QTc Interval (ms)	464.44 ± 20.35	431.09 ± 32.29	0.001[a]

[a] T-test [b] Mann-Whitney Test
BPM: beat per minute, CIO: Cardiac Iron Overload, ms: millisecond.
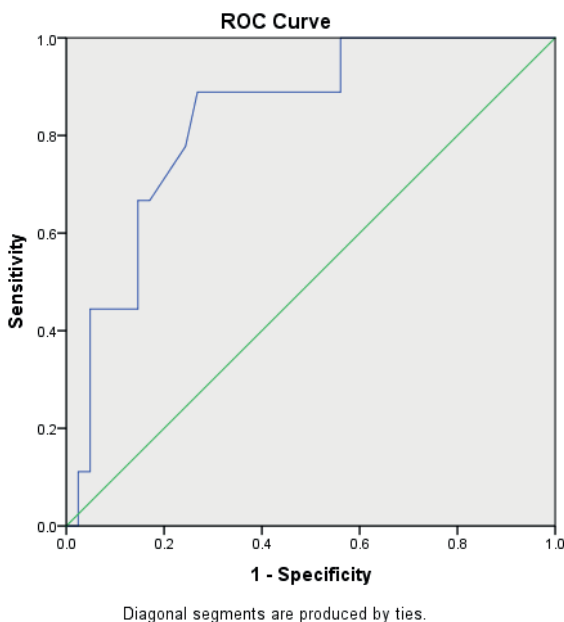
Fig. 1. ROC curve of QTc interval.

β-thalassemia patients. The most important finding of the present study is the difference of QTc interval in CIO and no-CIO adolescent β-thalassemia patients. Furthermore, we demonstrated that QTc interval had relatively good diagnostic value to diagnose CIO.

Patients with iron overload cardiomyopathies experience heart failure with systolic and diastolic dysfunction often in combination with electrical rhythm disturbances, including slowed electrical conduction, heart block, and the increase likelihood of having atrial fibrillation.[14,27] Iron overload cardiomyopathies are marked by early diastolic dysfunction which precedes systolic dysfunction.[14,27] Conventional echocardiography examination in this study was all normal indicating that all patients were at the early stage of the disease.

Electrical rhythm disturbances recorded in CIO in previous studies are mostly non-specific, typically associated with repolarization abnormalities and relative bradycardia.[25] QT interval as a mean of identifying depolarization and repolarization abnormalities are highlighted in our study. Recent meta-analysis showed

that thalassemia patients have prolonged QT interval compared to healthy controls.[17] The relationship between QT parameters and iron overload measured by serum ferritin had been studied previously with conflicting results.[24,28] Ulger et al.[28] found no correlation of QT parameters (QT interval, QTc interval, and QT dispersions) with serum ferritin levels while Faruqi et al.[24] showed QT interval, QTc interval, and QT dispersion are prolonged in patients with high serum ferritin level (>2500 ng/ml). Although serum ferritin was traditionally used as a marker for iron overload, it does not necessarily represent tissue's iron content since its level is influenced by many factors including infections. Furthermore, ferritin level is measured from the blood and not from any organ such as the heart, therefore it may not reveal its real level in the heart. In this study we measured directly focused to the heart by ECG and cardiac MRI, which shows obvious correlation between MRI and ECG results.

Measuring cardiac iron loading has become possible using MRI T2*, and well corellated with cardiac iron loading in vivo.[19,20] The relationship between electrocardiographic recording and cardiac MRI T2* has been prevously studied.[25] Detterich et al.[25] found that repolarization indices were the most sensitive discriminators and QT interval was greater in patients with CIO.[25] In our study, mean QT interval was not statistically different but QTc interval was significantly increased in CIO patients. Although Detterich et al.[25] had also found a significantly longer QTc in patients with detectable cardiac iron they did not exclusively include adolescents. Our study specified in adolescent patients which may or may not be valid for other age groups. Besides QT parameters, other repolarization abnormalities such as ST and T wave abnormalities may be found in CIO patients which was not focused in our study. QT prolongation in thalassemia patients may be secondary to compensatory ventricular dilation and increased circulatory oxidative species caused by labile plasma iron.[29,30] In

an animal model, CIO was characterized by a decrease of the overshoot and duration of action potential and impairment of delayed rectifier potassium channel.[33] CIO is also associated with bradycardia which may arise from altered intrinsic sinoatrial node function.[34] The number of patients with bradycardia was not different between two groups in our study which may be due to small sample size or relatively early stage of the disease.

The relatively good diagnostic value of QTc interval with high sensitivity might lead to the use of QTc interval as a screenig tool. The QTc interval prolongation perhaps could be regarded as a surrogate marker of MRI T2* to detect cardiac iron overload especially in the adolescent group. It is indeed much cheaper, widely available and could be done by the majority of health personnel. It is needed in areas where thalassemia is of high prevalence with limited resources. However, larger sample size and multi center study may be needed to support the results

Cardiac iron overload is associated with QTc prolongation in the adolescent. The QTc interval value of 449 ms might be used as a cut off point of cardiac iron overload.

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