Assessment of the relationship between fragmented QRS and cardiac iron overload in patients with beta-thalassemia major

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Abstract

Objective: Beta-thalassemia major (TM) is a genetic hemoglobin disorder causing chronic hemolytic anemia. Since cardiac insufficiency and arrhythmias are the primary causes of mortality in such patients, monitoring of cardiac iron load is important in management of the disorder. The purpose of this study was to investigate the importance of fragmented QRS (fQRS) and its relation to the cardiac T2* value for the evaluation of cardiac iron load in TM patients.

Methods: This retrospective study included 103 TM patients. The patients' T2* values, measured by cardiac MRI and 12-lead surface ECGs, were interpreted. The cardiac T2* values under 20 were considered as cardiac iron overload. The relationship between the cardiac T2* value and fQRS in ECG was investigated.

Results: The median age of the patients was 22.6±6.6 years. All patients were on regular blood transfusions and iron chelators. The patients had no risk factors for coronary artery disease. In 50 (48%) patients fQRS was detected, and in 37 (74%) of these the T2* values were low. 86% of patients with cardiac involvement (37) had fQRS, but 22% of patients with non-involvement (13) had fQRS ($p<0.001$).

Conclusion: Since cardiac involvement is the primary cause of mortality in TM patients, the early diagnosis of cardiac dysfunction is of vital importance. The search for fQRS in the ECGs of these patients, particularly when cardiac T2* values cannot be determined and followed, is a non-expensive and easy-to-attain method for therapy management. *(Anatolian J Cardiol 2015; 15: 132-6)*

Key words: beta-thalassemia major, electrocardiography, fragmented QRS, cardiac MR imaging, T2* value

Introduction

Beta-thalassemia major (TM), is a frequently encountered monogenic disorder that decreases the synthesis of globin, a protein component of hemoglobin. TM patients require repeated blood transfusions because of deep anemia due to ineffective erythropoiesis (1). Peripheral hemolysis, the increased intestinal absorption of iron, ineffective erythropoiesis, and, most importantly, repeated blood transfusions cause an overload of iron in the body (2). Iron accumulation starts in the reticuloendothelial system (RES). The iron saturation of RES is followed by iron accumulation in other organs, namely, endocrine glands, liver and myocardium. In TM patients, myocardium is not the first site of iron accumulation, but it is the organ where the most serious complications occur (3, 4).

In TM patients cardiac insufficiency and arrythmias, due to cardiac iron overload, are the major causes of mortality (5). Thus, cardiac MRI and regular measurements of the T2* value are recommended for evaluating cardiac iron load (6). However, since MRI is expensive and not easily attained for early diagnosis of cardiac dysfunction, more practical methods have been sought.

In recent studies, the presence of fQRS at the surface ECG has shown to be related with conditions leading to myocardial activation nonhomogeneous (7). Cardiac iron overload and fibrosis in patients with TM, may result in a non-homogeneous activation. This study was planned to investigate the relationship between fragmented QRS (fQRS), observed in non-homogeneous cardiac activations like scar formation and fibrosis, and cardiac iron overload and so to cardiac T2* value in patients with TM.

Methods

This retrospective study included 103 TM patients between 15 and 40 years of age who were followed at our Center for

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Thalassemia. Patients with diabetes mellitus, hypertension, ischemic heart disease and smokers were excluded, beside individuals were excluded from the study, if they had a history of coronary artery disease or regional wall motion abnormalities under resting transthorasic echocardiography examination. Patients were divided into four different treatment groups of deferiprone, deferoxamine, deferiprone+deferoxamine combination, deferasirox and were receiving the same treatment regimen for at least two years. The annual cardiac MR T2* values and annual ECGs of the patients were evaluated. The patients' 12-lead surface ECGs were analyzed for the presence of fQRS (Nihon Kohden-Cardiofax S ECG-1250K, filter range 0.5Hz to 150Hz, AC filter 60Hz, 25 mm/s,10 mm/mV). The fQRS pattern was identified by the presence of different RSR' patterns in the presence or absence of the Q wave in two adjacent derivations (QRS duration, <120 ms); additional R wave (R' wave) or notching in the nadir of the R or S wave or by the presence of more than one R wave in the absence of typical bundle branch block (7). The measurement of cardiac MR T2* was evaluated according to the description by Westwood et al. (8). The cardiac T2* value <20 ms was accepted as cardiac iron overload. The relationship between the cardiac T2* value and fQRS in ECG was investigated.

Statistical analysis

Data were analyzed with the SPSS software version 15.0 for Windows. Categorical variables were presented as frequency and percentage. The χ^2 test and Fisher's exact test were used to compare categorical variables. The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Student's t-test was used for variables with normal distribution and the values were presented as mean±SD. Continuous variables without normal distribution were analyzed using Mann-Whitney U test and obtained values were presented as median (50^{th}) values and interquantile ranges (25^{th} and 75^{th}). Multivariate logistic regression analysis was used to evaluate the independent associates of the risk of cardiac involvement. Parameters with a p value of less than 0.1 in univariate analysis were included in the model. The odds ratios (OR) and 95% confidence intervals (CI) were calculated. A two-tailed p value of <0.05 was considered statistically significant.

Results

The study included 103 patients with TM of whom 46 were males. The median age of the patients was 22.6±6.6 years. All patients were on regular blood transfusions and iron chelators. Patients had no risk factor other than smoking for coronary artery disease. Between the groups with and without cardiac involvement, there was no difference in left ventricular ejection fraction, age, gender (Table 1). The study showed the presence of a significant relationship between cardiac T2* value and fQRS in ECG. In 50 (48%) patients fQRS was detected and in 37 (74%) of these the T2* value was found low. 86% of patients with cardiac involvement (37) had fQRS, but 22% of patients with non-involvement (13) had fQRS (p<0.001) (Fig. 1). Mean age of patients with fQRS was 24.4±7.7 years, while those without fQRS was 21.4±6.6 years (p=0.01). Between the groups with and without fQRS, there was no difference in left ventricular ejection fraction and sex.

In logistic regression analysis for cardiac iron overload, significant correlation was found in univariate analysis (OR, 22.3; 95% CI, 7.7-64.3; p<0.001) and multivariate analysis (OR, 19.0; 95% CI, 5.2-69.7; p<0.001) between the presence of cardiac iron overload and the presence of fQRS. Univariate analysis are used according to types of iron chelates, deferoxamine or deferasirox users compared with non-users have a low incidence of cardiac

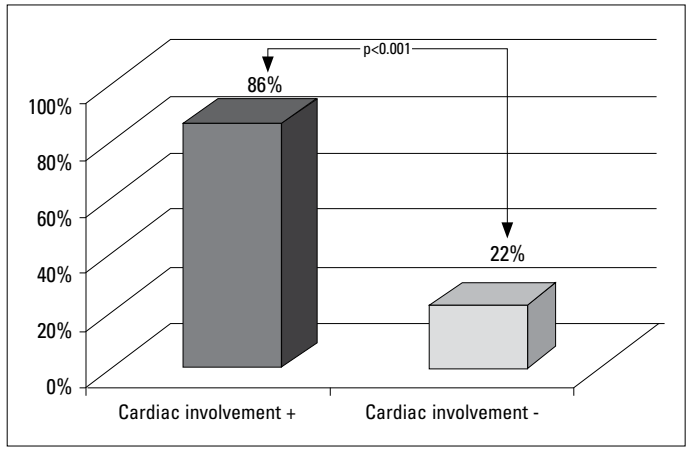

Figure 1. Patients with cardiac involvement, have been seen more frequently in the presence of fQRS

Table 1. Demographic characteristics with and without cardiac involvement

Variables	Cardiac involvement (+) (n=43)	Cardiac involvement (-) (n=60)	*P*
Age, years	22 (20-27)	21 (18-25)	0.299
Male gender, n (%)	19 (44%)	27 (45%)	0.935
Trigliseride, mg/dL	165±93	122±46	0.003
LDL, mg/dL	68±37	54±24	0.029
HDL, mg/dL	28±11	30±10	0.384
Total cholesterol, mg/dL	128±47	110±29	0.019
Hemoglobin, g/dL	8 (8-9)	8 (8-9)	0.634
WBC, $10^3/mm^3$	10 (6-25)	8 (6-17)	0.278
PLT, $10^3/mm^3$	418±218	405±224	0.775
EDD, mm	45±4	47±4	0.020
ESD, mm	28±4	30±4	0.050
LVEF, %	60 (58-65)	60 (60-65)	0.214
fQRS present	37 (86%)	13 (22%)	<0.001
T2* value	13±3	33±10	<0.001

Which show a normal distribution mean±SD, not show a normal distribution median 25. and 75. percentile EDD - left ventricular end-diastolic diamater; ESD - left ventricular end-systolic diamater; LVEF - left ventricular ejection fraction; WBC - white blood cell

Table 2. In univariate regression analysis, were investigated which is associated with cardiac involvement cases and fQRS was significantly correlated with the presence of cardiac involvement

Variables	OR	95% CI	*P*
fQRS present	22.3	7.7-64.3	<0.001
Deferiprone	1.85	0.82-4.18	0.141
Deferoxamine	2.73	1.21-6.14	0.015
Deferiprone+Deferoxamine	2.46	0.94-6.43	0.067
Deferasirox	0.38	0.17-0.87	0.021

Table 3. Iron chelates used in association with cardiac involvement were evaluated

Variables	Cardiac involvement (+)	Cardiac involvement (-)	*P*
Deferiprone	19 (44%)	18 (30%)	0.139
Deferoxamine	24 (56%)	19 (32%)	0.012
Deferiprone+Deferoxamine	13 (30%)	9 (15%)	0.054
Deferasirox	13 (30%)	32 (53%)	0.016

Table 4. Iron chelates used in association with the presence of fQRS, were evaluated

Variables	fQRS (+) (n=50)	fQRS (-) (n=53)	*P*
Deferiprone	22 (44%)	15 (28%)	0.097
Deferoxamine	30 (60%)	13 (25%)	<0.001
Deferiprone+Deferoxamine	14 (28%)	8 (15%)	0.110
Deferasirox	12 (24%)	33 (62%)	<0.001

Table 5. In multivariate regression analysis for fQRS, cardiac iron overload was significantly correlated with the presence fQRS

Variables	OR	95% CI	*P*
Age (For every 1 year)	1.064	0.993-1.141	0.079
Deferiprone	0.320	0.059-1.750	0.189
Deferoxamine	0.903	0.157-5.190	0.909
Deferasirox	0.087	0.008-0.941	0.044
Cardiac involvement	27.488	8.170-92.481	<0.001

involvement was seen more (Table 2). In deferoxamine or deferasirox users, cardiac iron overload is less than non-users, fQRS presence of these patients also have been seen less (Table 3, 4).

Multivariate logistic regression analysis was used for the presence of fQRS and cardiac iron overload was significantly correlated with the presence fQRS (OR, 27.4; 95% CI, 8.170-92.481; p<0.001). The relationship was detected at the border for used iron chelator deferasirox, there was no difference for the other medications (Table 5).

Discussion

This study has shown that in patients with TM the presence of fQRS in surface ECG is associated with a decrease in cardiac T2* and thus with cardiac iron overload. The quantity of iron overload varies greatly, but is highest in the subepicardium followed by subendocardium, frequently yielding a patch-like image (9, 10). The accumulation occurs mainly in the myocardium (particularly in the interventricular septum and ventricular free wall) rather than in the atrioventricular conduction system (11).

Studies with tissue Doppler imaging (TDI) or radionuclide angiography have shown regional non-uniformity of left ventricular wall movement even in the early stage of iron accumulation, a finding which indicates that in the myocardium, iron is deposited non-homogenously and in a patch-like pattern. However, TDI and radionuclide angiography cannot assess the cardiac iron content (12, 13). For the evaluation of cardiac iron overload, cardiac MR and measurement of T2* value are recommended. Studies have shown that cardiac T2* is highly predictive over 1 year for the development of heart failure and arrhythmia. Low T2* values are associated with the occurrence of myocardial dysfunction. A study involving 652 patients with TM has reported that cardiac T2* values of <20 ms are significantly associated with the risk of arrythmia and for patients with T2* values of <10 ms with risk of cardiac insufficiency (14).

Cardiac iron overload first leads to delay or blockage in myocardial electrical conduction and later to disorders in myocardial contraction. In the early stage of the disorder, as criteria, bradycardia, changes in ST-T, seldom atrial and ventricular premature systoles, first-degree atrioventricular block, and left ventricular hypertrophy are observed (15, 16). In the late stage of the disorder, frequent atrial and ventricular premature systoles, supraventricular tachycardia, second-degree or complete cardiac block can occur (5, 16). Additionally, prolongation of QT and PR intervals subsequent to slowing of conduction in cardiac muscle has been reported (17). Kuryshev et al. (18) reported the presence of increased QT dispersion in 14 of 24 TM patients. Another study (19) has shown that ventricular late potentials (VLP) are more frequent in TM patients and that ventricular premature systoles and transient ventricular tachycardia occur more often in those with VLP. A recent study (20) has reported that the P wave dispersion, the free predictor of atrial fibrillation, is prolonged and associated with cardiac T2* value in such patients.

Among TM patients, cardiac insufficiency usually develops in those receiving inadequate chelation therapy. Excess free iron that cannot be further deposited in the lysosomes of myocytes exerts a toxic effect on the cell; it impairs the redox reactions and gene modulations, directly interacts with ion channels, stimulates the production of free radicals, and leads to oxidative membrane impairment. As a result of the impairment of energy production within mitochondria, cardiac dysfunction occurs (21, 22). Under normal conditions myocytes tonically suppress fibroblast proliferation, but this paracrine effect is reduced by myocyte iron loading. This observation explains the mechanism for iron-induced cardiac fibrosis in TM patients (23).

In a study on the evaluation of myocardial scar in 115 TM patients by delayed enhancement (DE) cardiac MRI (24), DE

areas were detected in 28 patients (24%) and in 26 of these patch-like fibrosis was observed. The study further reported that since the patients with scar formation were older than the others, myocardial fibrosis/necrosis was more frequent in TM patients than in normal individuals and that this situation is a time-dependent process and associated with KV risk factors (24). In our study, we also found that the incidence of fQRS increased with age, supporting time-dependent fibrosis. Another investigation by Kirk et al. (25) reported that in TM patients, macroscopic myocardial fibrosis was seldom observed and that fibrosis could be microscopic and reversible in such cases. Another study (26) reported that the characteristic histopathological finding in iron overloaded organs was iron deposit and/or interstitial fibrosis.

Since the main cause of mortality in TM patients is cardiac insufficiency, the early diagnosis of cardiac dysfunction and the modification of therapy accordingly are of utmost importance. Such patients can have regional non-uniformity of left ventricular wall movement as an early sign of cardiac involvement in spite of intact global ventricular function. A study on the early diagnosis of cardiac dysfunction by TDI in asemptomatic TM patients (27) showed regional systolic dysfunction of the lateral free wall and regional diastolic dysfunction in the septal and right ventricular wall. Another investigation with TDI (28) reported a significant relationship between the presence of fQRS and impairment of TDI parameters in TM patients.

The mechanisms for the development of fQRS have not been fully clarified. However, fQRS has been shown to be related to conditions of non-homogeneous depolarization, namely, myocardial scar, fibrosis or ischemia (29-33). In research, the presence of fQRS has been reported to be helpful in the evaluation of arrhythmic events and cardiac risk in different patient groups. The study which includes patients presenting with ST-segment elevation myocardial infarction, the presence of fQRS in application of ECG, may help to identify high-risk cardiac patients have been reported (34). In another study which includes patients with coronary artery disease, the presence of fQRS on ECG in patients with prior CABG, has been shown to have a higher risk of developing AF in the postoperative period (35). Also in researches in patients with arryhtmogenic right ventricular dysplasia (ARVD) and hypertrophic cardiomyopathy, presence of fQRS on the surface ECG, is reported to be a predictor for arrhythmic events (36, 37).

Iron overload and fibrosis in TM patients can cause non-homogeneous activation. In our study, the presence of fQRS on surface ECG, have been associated with cardiac iron overload. In view of this finding, during patient follow-up the emergence of fQRS in surface ECG is critical and would require the revision of treatment regimens. Also the presence of a significant relationship between age and the presence of fQRS and low T2* values upholds the theory that cardiac iron load increases parallel to age. An annual cardiac MRI is advised for MR patients under follow-up care. Additionally, a surface ECG to seek fQRS made at the time of visit for blood transfusion would contribute highly to the early diagnosis of cardiac dysfunction and evaluation of the outcome of treatment.

Study limitations

Since the study did not include the follow-up of the cases, the effect of fQRS on the prognosis could not be evaluated.

Conclusion

In TM patients the presence of fQRS in surface ECG has a high predictive value for cardiac iron overload. The detection of fQRS could be indicative of the need for closer monitoring and aggressive chelation therapy.

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