

Evaluation of QT parameters in patients of thalassaemia major with iron overload

Amna Faruqi,¹ Syed Imran Ahmad,² Syed Tousif Ahmed³

Abstract

Objective: To study QT parameters in Thalassaemia Major patients and their association with serum ferritin levels.

Methods: This cross-sectional study was conducted at Ziauddin University, Karachi, from February 2013 to September 2014, and comprised patients of Thalassaemia Major. Participants' serum ferritin levels were determined and electrocardiography was performed. Data was analysed using SPSS 20.

Results: Of the 135 participants, 68(50.4%) were in the 7-14 years age group and 69(51%) were males. Significant prolongation of QT, corrected QT interval and increased QT dispersion was observed in patients with serum ferritin levels more than 2,500 nanogram/millilitre ($p < 0.001$ each). These measurements of corrected QT and QT dispersion had a positive linear correlation with serum ferritin levels ($r = 0.760$ and 0.786).

Conclusion: Electrocardiography could be a useful means for the pre-clinical detection of cardiac involvement due to iron overload in Thalassaemia Major patients.

Keywords: Thalassaemia major, TM, Iron overload, Cardiac iron, Ferritin, QT interval. (JPMA 66: 799; 2016)

Introduction

Beta Thalassaemia Major (TM) is an inherited disease in which the patient requires regular blood transfusions (BTs).^{1,2} As a consequence of repeated BTs, iron overload (IO) starts to take place.³ Deposition of iron in the heart leads to cardiac complications which are the main causes of death in such patients.⁴ A clinical evaluation of these patients is not useful to detect this pathology in its early phase because IO of the heart becomes clinically apparent only when sufficient damage to the heart has taken place. Magnetic resonance imaging (MRI) is the gold standard for pre-clinical detection of IO in the heart of patients who have an, otherwise, normal cardiac function.⁵ However, many countries, including Pakistan, do not have easy availability of cardiac MRI T2* facilities. And even if available, they are extremely costly and time consuming. Early detection of cardiac IO and early commencement or stepping up of chelating treatment is important for the health and life of patients. Studies have been conducted to determine the usefulness of electrocardiography (ECG) in detecting cardiac IO, with variable results. In Pakistan, to the best of our knowledge, no study has been conducted on the electrocardiographically observed changes in Beta TM patients and their association with iron load.

The current study was planned to investigate a non-invasive, cost-effective and readily available method for the early detection of cardiac involvement due to IO, because once clinical manifestations of cardiomyopathy appears, it

is not possible to reverse the damage that has occurred.

We electrocardiographically observed QT parameters and their association with serum ferritin levels.

Patients and Methods

This cross-sectional study was conducted at Ziauddin University, Karachi, Pakistan, from February 2013 to September 2014, and comprised diagnosed patients of Beta TM who were selected using simple random convenient sampling from the Fatimid Foundation, Karachi. Diagnosis was based on the usual haematological criteria of peripheral blood film and haemoglobin (Hb) electrophoresis. Minimum age was seven years. Patients were receiving at least eight BTs per year (defined as chronic current transfusion therapy⁶). Those who did not give consent, suffered any other haemoglobinopathy, acute illness, some known congenital or acquired heart disease (e.g. coronary artery disease, hypertension, congestive cardiac failure, arrhythmias, heart blocks.), or were using drugs that lengthen the QT interval (e.g. antidepressants, antihistamines, antibiotics etc) were excluded. Patients who had used antiarrhythmics (e.g. Amiodarone) in the preceding six months were also excluded, as were patients with thyroid, renal or severe liver disease, diabetes mellitus (DM) and bone-marrow (BM) transplantation. After getting approval from the institutional review committee, patients were studied just prior to receiving BT. History of the patients' height, weight, pulse rate and blood pressure were all noted.

Electrocardiography was performed using ECG machine 901 (Zhuhai Kaden Yasen Medical Electronics Co., Ltd) at a paper speed of 25mm/sec. All intervals and axes were taken from standard ECG software and the intervals were

^{1,3}Department of Physiology, ²Department of Cardiology, Ziauddin University, Karachi, Pakistan.

Correspondence: Amna Faruqi. Email: dr_amnafaruqi@hotmail.com

double-checked manually by the principal investigator. Heart rate was calculated from the average RR interval of the lead II tracings.⁷ For each lead, three consecutive QT intervals were measured and averaged.³ QT dispersion (QTd), the difference between the longest and shortest QT intervals, was calculated.⁸ Corrected QT interval (QTc) was calculated using Bazett's formula ($QTc = QT/\sqrt{R-R}$ interval).^{3,7,8}

An analysis of serum ferritin was performed by Chemiluminescent Micro-particle Immuno-Assay (CMIA) technology using automatic immunoanalyser (ARCHITECT i2000SR; Abbott Laboratories). The normal range of serum ferritin (SF) was taken as 18-323 ng/ml.⁷

Severity of IO was defined by serum ferritin, which is the most commonly-used parameter for this purpose.⁹ Therefore, patients were divided into three groups. Group I had patients with SF < 2,500ng/ml; Group II had patients with SF levels ranging from 2,500-5,000ng/ml; and Group III had patients with SF > 5,000ng/ml.

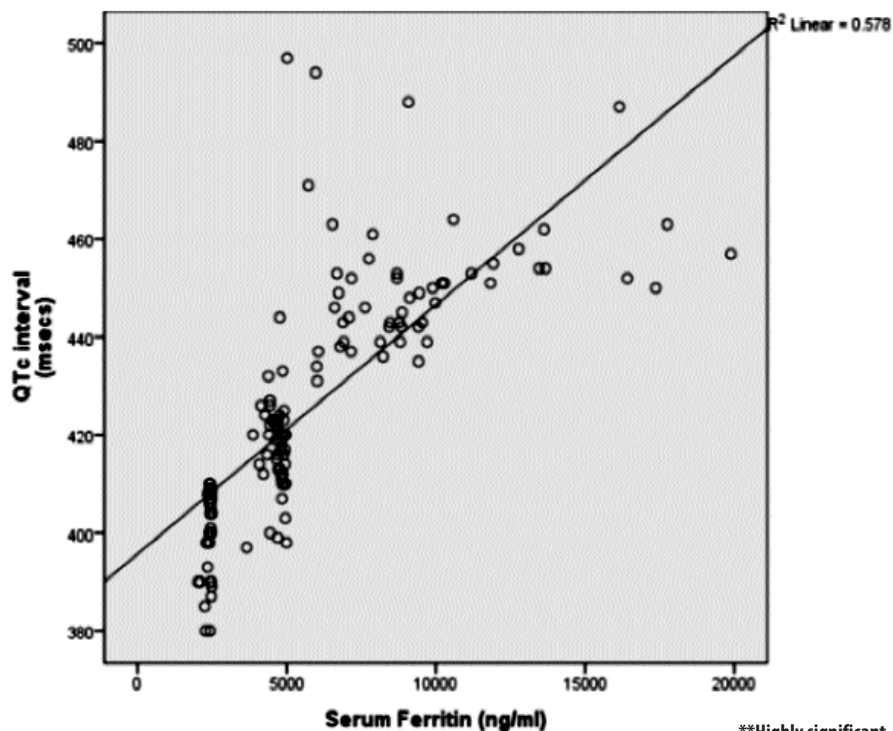
SPSS 20 was used for data analysis. For categorical variables, frequencies and percentages were calculated. For quantitative variables, mean with standard deviation was calculated, and Student's t-test was applied to determine significance. Pearson's correlation test was applied to study

the association between SF, QTc and QTd. P<0.05 was considered significant.

Results

Of the 135 patients, who were aged between seven and 30 years, 68(50.4%) were in the 7-14 age group. Males constituted 69(51%) of the participants.

The mean ferritin level was 6062.61±3641.796ng/mL. There was no significant difference in terms of gender (p=0.366).



**Highly significant.

Figure-1: Correlation graph between Serum Ferritin and QTc (r =0.760**).

Table-1: Intervals observed on ECG of study subjects.

	Group I N =33(24.5%)	Group II N=48(35.5%)	Group III N =54(40%)	P1	P2
Heart Rate (bpm)	98.9 ± 15.2	97.4 ± 14.8	97.8 ± 11.7	p=0.658	p=0.705
R-R interval (secs)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	p=1	p=1
PR interval (m sec)	141.0 ± 11.9	134.9 ± 15.6	137.2 ± 20.4	p=0.061	p=0.333
P wave duration (m secs)	108.5 ± 8.2	104.7 ± 11.7	104.7 ± 13.0	p=0.111	p=0.136
QRS duration (m secs)	85.7 ± 10.7	86.01 ± 7.8	89.1 ± 8.7	p=0.880	p=0.109
T wave duration (m secs)	153.9 ± 16.9	151.7 ± 15.6	157.5 ± 21.5	p=0.548	p=0.415
QT interval (m secs)	315.7 ± 22.4	332.8 ± 23.2	352.9 ± 21.7	p=0.0014**	p=0.0001**
QTc interval (m secs)	399.2 ± 8.9	417.3 ± 9.1	451.5 ± 14.3	p=0.0001**	p=0.0001**
QTd (m secs)	12.1 ± 6.5	20.2 ± 8.4	40.4 ± 9.5	p=0.0001**	p=0.0001**

P1=Gp II compared with Gp I. P2=Gp III compared with Gp I.

Group I: Ferritin level < 2,500ng/mL. Group II: Ferritin level 2,500-5000ng/mL. Group III: Ferritin level > 5,000ng/mL

QTc: Corrected QT.

QTd: QT dispersion.

**highly significant.

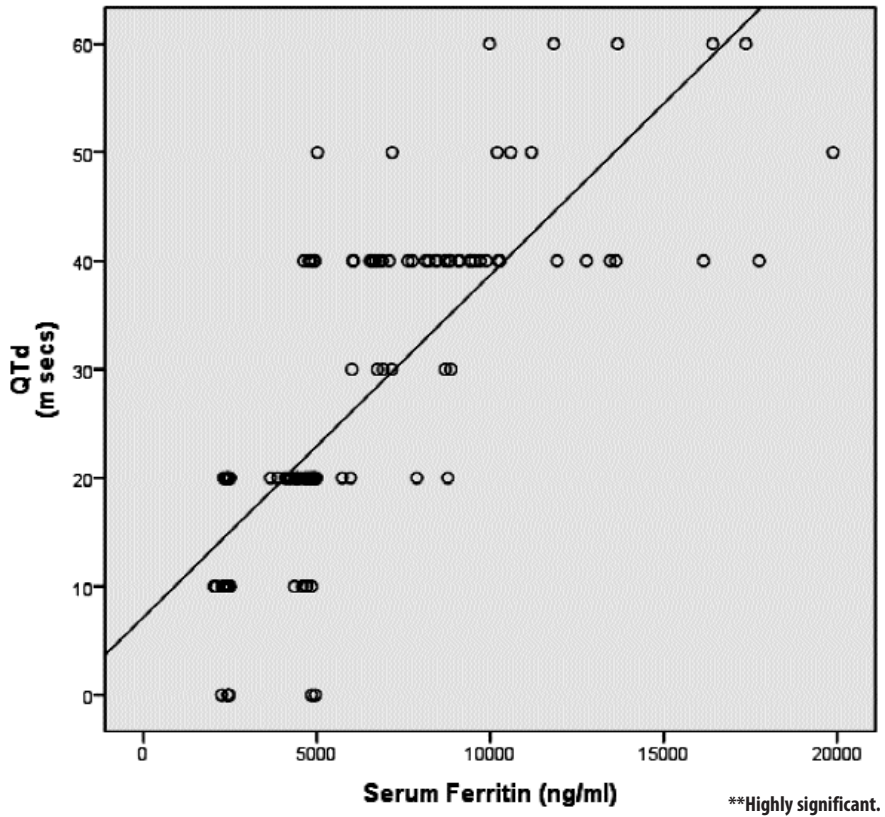


Figure-2: Correlation Graph between Serum Ferritin and QTd ($r = 0.786^{**}$).

Table-2: Comparison of QT interval prolongation according to age & gender.

Patients with QT prolongation	Age Groups			P value
	7-14 years (n=68)	15-22 years (n=57)	23-30 years (n=10)	
Male	10	5	-	0.377
Female	4	12	3	0.025

Group I included 33(24.5 %) patients; Group II 48(35.5%); and Group III comprised 54(40%) patients. QT, QTc and QTd were all significantly increased in Group II ($p=0.0014$; $p=0.0001$; $p=0.0001$) and Group III ($p=0.0001$ each) when compared with Group I (Table-1). There was no significant difference in other intervals among the three groups ($p>0.05$). Moreover, increasing age was significantly associated with QT prolongation in females ($p=0.025$) (Table-2).

A significant positive linear relation was observed between SF level, QTc and QTd ($p=0.01$) ($r=0.760$ and $r=0.786$) (Figures-1,2).

Discussion

Involvement of the heart in Beta TM is a significant problem

which results in increased morbidity and mortality. Patients getting regular BT receive about 20 times the customary intake of iron. This excess is the main cause of subsequent damage to the heart, endocrines, liver and other organ tissues.⁷

TM patients show a markedly poor survival rate after the first decade of life.^{10,11} Similar results were obtained in ours and some previous studies.^{11,12} A better prognosis for survival without cardiac disease is seen in TM patients receiving regular BT, in which SF levels remain below 2,500ng/ml.¹³ The mean SF of our subjects was higher than that recorded in other studies and this may be the possible reason for the increased frequency of cardiac complications in our population and lower life expectancy. Lower mean SF levels have been recorded in various studies.^{1,11,14} The high mean SF of our study sample may be due to the difference in the standard of health care being provided to our patients, non-affordability of chelation therapy by many, and a poor availability of infusion pumps. However, a study conducted in India recorded a much higher level.¹⁵

The QT interval is a means of identifying ventricular depolarisation and repolarisation. Its prolongation predicts a higher risk of fatal arrhythmias and sudden demise.¹ High intracellular iron causes disturbance in the function of the sodium channels responsible for the upstroke (depolarisation) of the cardiac action potential. On the other hand, the delayed rectifier potassium and calcium channel modification may be responsible for repolarisation abnormalities.^{9,16}

QTd is representative of variability of ventricular repolarisation¹⁷ and is an indicator of non-homogeneity of the myocardial repolarisation.⁷ An increased QTd value is a predictor of cardiac morbidity and mortality.⁶ In addition to causing dysfunction of ion channels, iron deposition in the myocytes also causes them to hypertrophy, and become ischaemic.¹⁸ This iron deposition followed by fibrosis is seen to occur in a non-uniform pattern in the heart, causing the myocardium to lose its homogeneity and be reflected as an increased QTd.¹⁹

In our study, prolongation of QT and QTc and an increase in QTd was observed in patients with high SF levels. These

results were in accordance with previous studies.^{3,6,7,18,20,21}

However, two studies apparently showed conflicting results,^{1,8} noting that conventional QT and dispersion parameters were prolonged in TM patients as compared to the controls, but statistical significance was not observed. A plausible explanation may be that since their patient group had a mean SF level well below the internationally accepted prognostic cut-off value of 2,500ng/mL,¹⁰ it was probably not high enough to produce significant changes in QT, QTc and QTd. Therefore, we may conclude that the results obtained in these studies were in accordance with our lowest SF group. Although the SF level in that group was higher than these two previous studies, it was still below the prognostic cut-off point, hence did not show QT prolongation like our higher SF groups.

Our study demonstrated a highly significant, positive linear correlation between SF level, QTc and QTd, showing that increasing SF levels may lead to greater level of iron deposition in the heart, ultimately giving rise to increasing extent of cardiac involvement. Previous studies concur with these results.^{5,7,21}

One of the limitations of our study was a small sample size. Moreover, due to budgetary constraints, we did not have an age- and gender-matched healthy control group.

Conclusion

Significant QT changes which correlated strongly with SF levels maybe indicative of early cardiac iron deposition. ECG could serve as a useful means for preclinical detection and monitoring of cardiac complications in patients of TM.

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Conflict of Interest: None.

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