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Original Article

Electrocardiographic Changes in Thalassemia Major Patients and their Association with Serum Ferritin Levels

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Abstract

Background: To evaluate the use of electrocardiography (ECG) in thalassemia major patients, for the early detection of iron overload induced cardiac complications.

Methods: Serum ferritin analysis and a standard 12 lead ECG was performed on 135 thalassemia major patients. SPSS Version 20 was used for data analysis. For categorical variables, frequencies and percentages were calculated. For quantitative variables, mean with standard deviation was calculated. Chi Square test was used for finding association between different ECG changes and serum ferritin levels. A p value of <0.05 was considered to be statistically significant.

Results: Patients ranged in age from 7-30 years. Males constituted 51 %. The mean serum ferritin level was 6062.61 ± 3641.796 ng/ml. There was no significant difference between the mean ferritin levels in males and females (p =0.366) One or more abnormal electrocardiographic findings were observed in 88.1% of patients. The most commonly observed findings were flattening of the T wave, followed by arrthymias, tachycardia, pathological T wave inversions, long QT interval, left ventricular hypertrophy (LVH) and right ventricular hypertrophy (RVH). Long QT interval was the only abnormality found to be significantly associated with high ferritin levels. (p =0.001).

Conclusion: ECG can be used for monitoring thalassaemia major patients for the development of cardiac complications, especially where magnetic resonance imaging (MRI) is not available

Key Words : Thalassemia Major, Iron overload, ECG, Ferritin

Introduction

Thalassemia is a monogenic disorder characterised by decreased synthesis of the globin chain; a component of hemoglobin .The most severely affected are the thalassaemia major (TM) patients, who despite regular blood transfusions still have poor prospects for survival.[1] According to the Thalassemia International Federation, the best way to transfuse these patients is by giving them group and type specific packed red cells. As a consequence of repeated blood transfusions, and excessive iron absorption from the gut, iron overload takes place. [2] Cardiac complications attributable to iron deposition in the heart are the foremost cause of death in these patients. [3] Thus, the purpose of iron chelation therapy is the prevention of cardiac iron deposition. Keeping serum ferritin and liver iron concentration at a low level are essential therapeutic goals, however, even so complete cardiac protection cannot be guaranteed.This study was performed with the aim of considering the use of ECG, in the early detection of cardiac involvement in thalassemia major patients, in countries with economic barriers to provision of affordable MRI facilities. [4,5]

Patients and Methods

A cross-sectional study was conducted at Ziauddin University after approval by the Ethics Review Committee of the University. A random selection of a hundred and thirty five TM patients coming for routine blood transfusion at the Fatimid Foundation, Karachi was carried out. Patients included in the study were 7 years of age and above, and receiving chronic transfusion therapy, which is defined as at least 8 transfusions per year.[4] All patients were on variable levels of chelation therapy. A patient was excluded from the study if he/she was found to have any acute illness, known congenital or acquired cardiac problems, severe liver, kidney or thyroid disease, diabetes mellitus, any other hemoglobinopathy, had undergone bone marrow transplantation or was receiving medication known to affect the length of the QT interval . Written, informed consent was taken from adult patients and in case of children, from their

guardians.History of each patient was taken, height and weight was recorded and examination for pulse rate and blood pressure was carried out prior to receiving blood transfusion. Serum Ferritin analysis was performed by chemiluminanse technique.

A standard 12 lead ECG was performed at a paper speed of 25 mm/sec, which was then studied for changes by a consultant cardiologist, who was blinded to the clinical status of the patient. Three successive ECG complexes were studied in each lead. Tachycardia was defined as a heart rate of more than 100/minute.[6] Long QT interval was defined as a corrected QT interval of more than 450 milli-seconds (ms) in males and more than 460 ms in females. Electrocardiographic criteria for left ventricular hypertrophy (LVH) was a sum of S V_1 and RV_5 voltages of more than 35mm.[6] Right ventricular hypertrophy (RVH) was diagnosed by R wave in the right precordial leads. [7] A patient was labelled as having pathological T wave inversion, if inversion was observed in at least two leads other than V_{1-3} which is considered to be normal juvenile pattern.[8]

The patients were divided into 3 groups on the basis of their ferritin levels: Group I comprised of 33 patients with ferritin level < 2500 ng/mL, Group II of 48 patients with ferritin level between 2500- 5000ng/mL, and Group III of 54 patients with ferritin level > 5000ng/mL .

For quantitative variables, descriptive statistics was used to calculate mean and standard deviation. A Chi Square test was used for finding association between different ECG changes and serum ferritin levels. P-value of <0.05 was considered to be statistically significant.

Results

In this study group of 135 patients of BTM, there were 51 % males. Patients' ages ranged from 7-30 years, and a large proportion (50.4%) were in the 7-14 year age group.The mean serum ferritin level of patients was 6062.61 $\pm$ 3641.796 ng/ml. There was no significant difference between the mean ferritin levels in males and females (6340.90 $\pm$3692.183ng/ml and 5771.67+ 3593.22 ng/ml, respectively). (p =0.366).Interpretation of electrocardiographic recordings revealed that one or more abnormal findings were observed in 88.1% of patients. (Table 1). Majority (91.3%) of male and 84.3 % of female patients showed ECG changes and the entire oldest age group(23-30 years) was affected. (Table 2) The most commonly observed finding was flattening of the T wave, followed by arrthymias, tachycardia, pathological T wave inversions, long QT interval, LVH and RVH .(Table3; Figure 1).

Table1:Beta Thalassaemia Major-Frequency of ECG changes

ECG Change/s	n= (135)	Percentage
Observed	119	88.1
Not Observed	16	11.9

Table 2: Beta Thalassaemia major-ECG changes according to gender and age

Demographic variables		No(%)
Gender	Male (n=69)	63(91.3%)
	Female (n=66)	56 (84.8%)
	Total (n=135)	119(88.1%)
Age groups (years)	7-14 (n=68)	58 (85.3%)
	15-22 (n=57)	51(89.5%)
	23-30 (n=10)	10 (100%)

Table 3: Beta Thalassaemia major - ECG changes observed * (n=119)

ECG Change	No	Percentage
T wave change-flattening	105	88.2
Arrthymias	62	52.1
Tachycardia	53	44.5
Pathologic T wave inversion	46	38.7
Long QT interval	34	28.6
LVH	18	15.1
RVH	4	3.4

*Patients often showed more than one type of ECG change

Table 4: Frequency of different ECG changes observed in three groups based on ferritin levels

	Group I Ferritin <2500ng/ml	Group II Ferritin 2500-5000ng/ml	Group III Ferritin >5000 ng/ml	p-Value
	n=33	n= 48	n= 54	
Sinus Bradycardia	0	0	0	--
Sinus Tachycardia	15	19	24	0.84
Sinus Arrthymia	17	28	28	0.76
Long QT interval	3	6	25	0.001**
T wave change(flattening)	28	37	40	0.497
Pathologic T wave inversion	9	16	24	0.235
Left Ventricular Hypertrophy	4	7	7	0.95
Right Ventricular Hypertrophy	1	3	0	0.39

**=highly significant

Comparison of the ECG changes of patients in the three ferritin groups (Table4) showed that long QT

interval was significantly associated with high ferritin levels (p =0.001) whereas no association was observed for the other ECG changes and ferritin levels (Table 4).

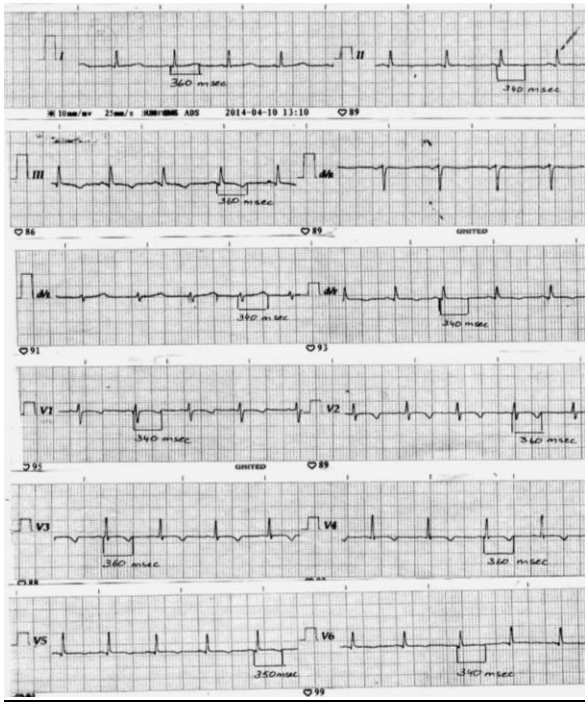

Figure 1: ECG of a beta thalassaemia major Patient: T-wave inversion in Leads III, aVF and V1-5, along with prolongation of the QT interval.

Discussion

This study adds to the work done, with regard to the use of electrocardiography in TM patients for the detection of cardiomyopathy due to iron deposition. The changes that take place due to iron deposition in the cardiac tissues of these patients, are degeneration, fibrosis, and dysfunction.[5] Improved prospects for survival, without cardiac disease, are observed in thalassemia major patients, receiving regular blood transfusions, when their serum ferritin levels remain below 2,500 ng /ml.[9]

T-wave flattening and inversion observed in these patients is believed to be indicative of cardiac ischaemia, while tachycardia may be explained as a physiological compensation for anaemia which exists in these patients.[4] The QT interval signifies ventricular depolarization and repolarization. [10] Increased levels of intracellular iron disrupts the function of the sodium channels which cause depolarization in the cardiac action potential. Repolarization abnormalities are also observed which are due to altered functioning of the delayed rectifier potassium and calcium channels.[1, 11] Prolongation of the QT interval predicts a higher risk of fatal arrthymias and sudden demise.[10] Hastened vascular aging and increased cardiac output, in thalassemia patients, have been suggested as reasons for left ventricular hypertrophy.[4,11] The right ventricular hypertrophy, observed in these subjects may be attributed to a gradually increasing pulmonary vascular resistance leading to the development of pulmonary hypertension.[11] Pulmonary arterial hypertension has been seen to have a prevalence of 6% in patients of thalassemia and sickle cell disease.[12]

Inversion of T- wave, tachycardia, and broad QRS complexes are important ECG signs of impending heart failure in patients with Thalassemia major, and the presence of at least two of these three changes gives a sensitivity of 81% and a specificity of 91% in predicting the development of heart failure.[13] Serum ferritin rise of 1000 ng/ml, increases the possibility of developing these ECG changes by 27- 40%.[13]

Conclusion

1. Electrocardiography can be used for monitoring TM patients for the development of cardiac complications, as myocardial iron load cannot be predicted from serum ferritin levels alone.
2. In the absence of T2*MRI , electrocardiography is an effective substitute to assess cardiac damage in beta thalassaemia major patients.
3. T- wave changes and QT interval prolongation are considered the most sensitive measure of iron loading.

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