Frequency And Significance of Electrocardiographic Changes in Beta Thalassemia Major Patients

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ABSTRACT

Objective: To find out the electrocardiographic changes among beta thalassemia major patients as the marker of cardiac complications at later stages of life.

Study Design: Prospective observational study.

Place and Duration of Study: Department of Pediatrics and Neonatology, Pak Emirates Military Hospital Rawalpindi from Jul 2018 to Dec 2018.

Methodology: One hundred and thirty patients of age 5-20 years with beta thalassemia major were included in the study. Patients were attending the thalassemia centre regularly.

Results: Out of total 130 patients, 70 (53.84%) were males and 60 (46.15%) were females. Out of 81 (56.92%) patients showed at least one electrocardiographic change while 49 (37.69%) patients showed normal electrocardiography. Remarkable electrocardiographic changes were sinus tachycardia, arrhythmias, T-wave inversions, long QTc interval and sinus bradycardia. There was statistically significant association in the increased serum ferritin levels, electrocardiographic changes, number of blood transfusions and occurrence of ECG changes (p<0.05).

Conclusion: Regular electrocardiographic monitoring has significant role in cardiac evaluation of beta thalassemia major patients as an indicator of evolving cardiac complications that can arise from iron overload secondary to multiple blood transfusions.

Keywords: Beta thalassemia major, Blood transfusions, Electrocardiography, Ferritin, Hemosiderosis.

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INTRODUCTION

The treatment of beta thalassemia major (BTM) has improved dramatically over the past two decades,[1] but still the clinical condition of patients remains to be the area of great diversity.[2] These patients need to be transfused with packed red blood cells on regular basis .[3] These numerous blood transfusions result ultimately in iron overload and deposition in various body organs including cardiac hemosiderosis. Iron overload is the primary factor of cardiac damage resulting in thalassemic cardiomyopathy.[4]

Cardiac disease is the major cause of morbidity and mortality among patients of thalassemia.[5] Careful analysis of electrocardiograms and using other non-invasive diagnostic modalities like echocardiography, 24 hrs Holter ECG monitoring and T2 MRI heart might help in the early identification of high-risk BTM patients for cardiac complications like cardiomyopathy, diastolic dysfunction, systolic impairment, arrhythmias, heart failure and sudden cardiac death.[4]

Monitoring cardiac function with echocardiography is the standard measure of care for BTM patients as diastolic and systolic dysfunction are later signs of iron overload.[6] In order to detect the pre-clinical iron deposition some thalassemia centers frequently observe their patients with cardiac MRI . Thus cardiac T2* has become the standard measure of care for the detection of pre-clinical cardiac iron deposition.[7,8]

Unfortunately, many medical centers do not have the resources to perform cardiac T2* measurements. Under-developed countries with economic barriers have limited resources and access to the frequent MRI use. Thus in situations where MRI is not available, changes in ECG variables can be very helpful to stratify cardiac risk. This study was planned to find out the electrocardiographic changes among beta thalassemia major patients as the marker of cardiac complications at later stages of life.

METHODOLOGY

This prospective observational study was conducted at the Department of Pediatrics and Neonatology, Pak Emirates Military Hospital Rawalpindi, from July

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to December 2018 after getting approval from Ethical Review Committee (A/28/EC-09). A Sample of 130 patients was selected through consecutive sampling from Thalassemia Centre in Military Hospital where these patients used to come for regular blood transfusions.

Inclusion Criteria: Patients of age 5-20 years with beta thalassemia major were included in the study.

Exclusion Criteria: Patients with acute illness and inflammatory condition of kidney or liver, patients with known congenital heart diseases or acquired cardiac morbidities, diabetes mellitus and thyroid diseases were not included in the study. Patients who were on the medication which could affect the QT interval e.g. antibiotics (Azithromycin, Clarithromycin, Metronidazole), antifungals (fluconazole, ketoconazole), antimalarials (chloroquine) and antiarrythmic drugs etc. were excluded from the study. Other hemoglobinopathies like thalassemia intermedia and sickle cell disease were also excluded from the study.

Sample size was calculated using an online calculator (openepi.com) considering confidence interval= 95%, absolute precision=8.0 and prevalence of abnormal ECG changes=51.6% from a previous study carried out by Neha *et al*, in India.[8] Patients were fully informed about the study and informed consent was taken from parents as well as the patients in case of older children and adolescents.

Data like; age (years), gender, age at time of diagnosis, signs and symptoms, recent serum ferritin level (ng/L) and number of blood transfusions per year (ml/kg/year) were recorded.

A 13 lead ECG was carried out at a paper speed of 25mm/sec, which was further considered for variations by a paediatric cardiologist who was blinded about the clinical position of the patient. In every lead, three consecutive ECG complexes were studied. Sinus tachycardia was recorded based on age based reference ranges. Sinus bradycardia was defined as a resting heart rate below the 2.5% percentile for age and sex. The normal QT interval is below 400-440ms.To eliminate the effect of heart rate on QT interval, corrected QT interval (QTc) was used which was calculated using Bezett's formula.[9,10] The QTc was considered prolonged if greater than 450 ms in male patients and 470 ms in female patients.[11] If T-wave inversions were observed in minimum two leads other than V1-V3 (which is usual juvenile pattern) a patient was considered as having pathological T-wave inversions but also taking into consideration that T-wave inversions are normal till 6 years of age.[12,13] Arrythmias which we included were bundle branch block, atrial fibrillation and ventricular and supraventricular tachycardias. Patients were divided into two groups (<3000 ng/L and >3000 ng/L) according to their serum ferritin levels which were recommended for disease monitoring every three to six monthly. Again patients were divided into two groups based on number of blood transfusions in last 1 year (<100 ml/kg/yr and >100 ml/kg/yr). Patients' signs and symptoms were observed and recorded i.e. pallor, bone pains, hepatosplenomegaly and flow murmur(detected by clinical examination and confirmed by 2d-echo).

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22. The chi-square test was used to find out the relationship among various ECG changes and serum ferritin levels, number of blood transfusions per year and signs and symptoms of the patients. The *p*-value <0.05 was taken statistically significant

RESULTS

Out of 130 patients, 70 (53.84%) were males and 60 (46.15%) were females. Majority of patients were under the 10 years of age, with the mean age of 11 ± 2.4 years. Out of total 130 patients, 81 (56.92%) showed the presence of ECG changes while 49 (37.69%) showed normal ECG with no change.

Among 81 patients having ECG changes; 39 (48.14%) were males and 42 (51.85%) were females. In the patients having ECG changes; 23 (17.69%) patients had long QTc interval, 36 (27.69%) showed T-wave inversions, 49 (37.69%) had sinus tachycardia, 16 (12.30%) had arrhythmias and 6 (4.6%) patients had bradycardia (Table-I).

Table-I: ECG changes along with mean serum ferritin levels.

ECG changes	Patients n (%)	Mean Serum Ferritin Level (ng/L)
Sinus tachycardia	49 (37.69%)	2900 ± 1150.40
T-wave inversions	36 (27.69%)	3550 ± 1880.54
Long QTc interval	23 (17.69%)	4190 ± 1040.67
Arrythmias	16 (12.30%)	5010 ± 1090.91
Sinus bradycardia	6 (4.60%)	3600 ± 830.33

Two groups were made based on the serum ferritin level; group-1 (<3000 ng/L) and group-2 (>3000 ng/L). There were 73 (56.15%) patients in group-1 and 57 (43.84%) patients in group-2. Significant association was found between serum ferritin levels and sinus tachycardia as well as long QTc interval and arrhythmias but no statistically significant association was

found among ferritin level and T-wave inversions as well as sinus bradycardia as shown in Table-II.

Table–II: Association between ECG changes and serum ferritin level.

ECG Changes	Group-1 Ferritin level (ng/L)	Group-2 Ferritin level (ng/L)	*p*-value
Sinus Tachycardia	18 (36.73%)	31 (63.26%)	0.028
T-wave inversions	16 (13.88%)	20 (86.11%)	0.258
Long QTc interval	7 (30.43%)	16 (69.56%)	0.025
Arrythmias	4 (25%)	12 (75%)	0.031
Sinus Bradycardia	2 (33.33%)	4 (66.66%)	0.407

Two groups were made on the basis of number of blood transfusions in a year; <100 ml/kg/yr and >100 ml/kg/yr. There were 47 (55.38%) patients who had received less than 100 ml/kg/yr of blood transfusions and 83 (44.61%) had received more than 100 ml/kg/yr of blood transfusions (Table-III).

Table-III: Association of serum ferritin level with number of blood transfusions.

Serum Ferritin Level (ng/L)	No. of Blood Transfusions <100 ml/kg/yr	No. of Blood Transfusions >100 ml/kg/yr	*p*-value
Group 1 <3000	44 (60.27%)	29 (39.72%)	0.013
Group 2 >3000	21 (36.84%)	36 (63.15%)	

Regarding symptomatology, our study showed significant association only between flow murmur and ECG changes as shown in the Table-IV.

Table-IV: Association between clinical features and ECG changes.

Clinical Features n (%)		F ECG changes n (%)	*p*-value
Pallor	122 (93.84%)	51 (41.80%)	0.268
Bone Pains	94 (72.30%)	33 (35.10%)	0.242
hepatosplenomegaly	109 (83.84%)	62 (56.88%)	0.064
Flow Murmur	78 (60%)	60 (76.92%)	0.015

DISCUSSION

Thalassemia is the utmost prevailing hereditary blood disorder in the entire world.[14,15] Ineffective erythropoiesis presents complications in beta thalassemia major patients which can be prevented by regular blood transfusion therapy but it can result in toxic iron deposition in heart and endocrine glands.[16] The major cause of morbidity and mortality in this population is congestive heart failure.[17]

Our study augmented the already conducted researches about the use of electrocardiography in beta thalassemia major patients. It showed the tools that might aid in assessing cardiovascular status in the patients of thalassemia.[11] In our study, minimum age of the diagnosis of beta thalassemia major was 5 months with progressive pallor being the most common symptom 122 (93.84%). This finding was consistent with the study done by Jassim *et al*. In their study carried out in Baghdad, they reported pallor being the most common symptom among thalassemics 140 (77%).[12]

In our study we did not find any significant association between gender and ECG changes (p= 0.105) as also documented earlier by Faruqi *et al*, in their study done in Pakistan in 2015 (p=0.366).[11]

Electrocardiographic changes which were observed in our study, had been well supported by previous study done by Jassim *et al*, showing ECG changes as 67.1%.[12] Similarly Faruqi *et al*, showed prevalence of ECG changes as 88.1%.[11]

Our study reported the presence of sinus tachycardia as the most frequently encountered ECG change 49 (37.69%) among 130 BTM patients and this was previously reported by Dipti *et al*, in their study done in India that tachycardia was the most common ECG change observed 24 (40%) among thalassemic patients.[8] Similarly Jassim *et al*, showed that sinus tachycardia being the most common ECG change 58 (52.25%).[12] However, on the other hand Faruqi *et al*, reported T-wave flattening being the most frequent change (105, 88.2%).[11] In contrast to this Detterich *et al*, in their study conducted in America reported long QTc interval as most commonly observed change.[13]

In our study we found significant association between serum ferritin level and ECG changes (p=0.017). This result was consistent with the study done earlier by Kouegnigan Rerambiah *et al*, in India.[17]

In our study, we also compared serum ferritin level with various ECG subgroups and found out their association. The most significant association was between serum ferritin and long QTc interval (p=0.025) and the sinus tachycardia (p=0.028). These results were the same as those reported in a previous study, showing significant association between serum ferritin and long QTc interval (p=0.0002).[13] Another study which was carried out in Pakistan by Faruqi *et al*, showed

significant association with serum ferritin level and long QTc interval (p=0.001).[11] One study carried out in USA, reported significant association between long QTc and serum ferritin level (p=0.001).[18]

Our study also found out statistical association between the serum ferritin level and number of blood transfusions (p=0.013), supporting the fact that increase iron overload particularly in heart leads to ECG changes alerting the physician about the cardiac complications which can occur at later stages of life.[19] Therefore, these patients must be monitored on regular intervals for cardiovascular status. Our result was consistent with another study carried out by Kouegnigan Rerambiah *et al*, who showed a significant association between chronic multiple blood transfusions and serum ferritin level (p=0.0001).[17]

We compared signs and symptoms of thalassemics with ECG changes and found out that only flow murmur had significant association with ECG changes (p=0.015) while rest of signs symptoms had insignificant association. The study done earlier in by Jassim *et al*, reported no significant association between signs and symptoms and serum ferritin levels (p=0.077).[12]

This study was conducted with the objective of possibility of ECG use as a pre-emptive measure for the early detection of cardiac morbidity in thalassemia major patients. Ideally T2* MRI should be done to trace any cardiac tissue deposition but the regions like ours, which is a resources constraint country, ECG can be used as an indicator to assess various diagnostic tools to detect early cardiac function abnormalities due to iron overload.

In summary, electrocardiographic changes are common in beta thalassemia major patients and some variables are more strongly associated with iron overload. Owing to lack of cardiac T2* MRI facility in most of thalassemia centres, ECG is the low-cost non invasive diagnostic modality of monitoring the cardiac complications in BTM patients and ECG can be used in areas where there is high prevalence of thalassemia disease but have limited resources.

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RECOMMENDATIONS

There should be properly maintained record of serum ferritin levels done on regular basis as well as amount and interval of blood transfusions preferably in a record keeping diary form. Electrocardiography should be available in thalassemic units/hospitals. ECG monitoring should be done yearly/2 yearly beginning after 6yrs of age or as clinically indicated. Health education of patients' families should be carried out to ensure their cooperation in long life treatment.

CONCLUSION

Regular electrocardiographic monitoring has significant role in cardiac evaluation of beta thalassemia major patients as an indicator of evolving cardiac complications that can arise from iron overload secondary to multiple blood transfusions.

Conflict of Interest: None.

Authors Contribution

NH: Article writing, Data collection, MFS: Review of literature and data analysis, QUZ: Review of literature and methodology, HN: Article writing.

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