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Development of electrocardiographic anomalies and arrhythmias in adult beta-thalassemia major patients throughout the course of a brief follow-up

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ABSTRACT

Thalassemia major (TM) is an inherited blood disorder characterized by chronic anemia due to a lack of production of the necessary globin chains for hemoglobin. To ensure optimal survival, individuals with this condition require regular and ongoing blood transfusions and iron chelation therapy. Excessive iron accumulation can lead to cardiac siderosis, resulting in heart failure and irregular heart rhythms, which are the primary causes of mortality in TM patients. Therefore, it is crucial to identify early signs of cardiac involvement in thalassemia in order to provide preventive and therapeutic interventions. The objective of this study was to observe the progression of abnormal electrocardiographic patterns and arrhythmias in TM patients over a period of 12 months at a tertiary care hospital in India. All participants underwent 24-hour ECG Holter monitoring. The 24-hour recordings were carefully analyzed to identify different types of heartbeats (normal and abnormal), as well as any interference or artifacts. This suggests that the ECG repolarization and autonomic function issues in TM patients without obvious heart failure persist over a short-term follow-up period. While many of these events do not cause symptoms, the occurrence of supraventricular ectopy (abnormal heartbeats originating above the ventricles) and the burden of atrial fibrillation (AF) in this group seem to be severe and develop within a relatively short timeframe of 12 months. Therefore, it is crucial to closely monitor and detect arrhythmias in these patients. Future studies with longer follow-up periods and more comprehensive ECG monitoring will undoubtedly provide a clearer understanding of the specific impact and prognostic significance of certain ECG and arrhythmic markers in this particular context.

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INTRODUCTION

Thalassemia major (TM) is an inherited blood disorder that leads to chronic hemolytic anemia. It occurs due to inadequate production of the globin chains needed for hemoglobin synthesis. To ensure the best chances of survival, individuals with this condition require regular and ongoing blood transfusions as well as iron chelation therapy [1]. If left untreated, iron accumulation can lead to a condition called cardiac siderosis, which eventually results in heart failure and abnormal heart rhythms, known as arrhythmias. These cardiac complications are the primary causes of death among patients with

TM. Consequently, it is crucial to identify any hidden or subclinical cardiac involvement in thalassemia in order to implement preventive and therapeutic interventions [1].

Arrhythmia serves as an indicator of subclinical cardiac involvement in individuals with thalassemia major (TM), and several electrocardiographic (ECG) changes have been observed in TM patients without heart failure [2]. The utilization of Holter monitoring and fragmented QRS (fQRS) can help identify susceptibility to arrhythmias. Multiple studies have demonstrated a correlation between the presence of fQRS, which indicates abnormalities in depolarization, and an increased likelihood of developing arrhythmias. Additionally, cardiac magnetic resonance imaging (CMR) has revealed a connection between cardiac iron overload and the presence of fQRS in TM patients [2].

*Furthermore, r*educed heart rate variability (HRV), which serves as an indicator of cardiac autonomic function, can be assessed using 24-hour Holter monitoring. This parameter can be useful in the early diagnosis of iron overload cardiomyopathy in TM patients [3]. By monitoring HRV, clinicians can potentially detect early signs of cardiac complications related to iron overload in TM patients.

CMR-T2* is widely acknowledged as the most accurate technique and a powerful tool for early detection and monitoring of myocardial siderosis (iron overload in the heart), as well as for detecting small changes in the left ventricular ejection fraction. Various methods, including echocardiography, serum ferritin levels, heart rate variability (HRV), CMR-T2*, and liver and cardiac biopsy, have been examined for their effectiveness in the early detection of cardiac iron overload in TM patients. However, the findings from these studies have produced conflicting results [4].

An ideal diagnostic method for early detection of cardiac iron overload should be quick, noninvasive, affordable, and widely accessible. Unfortunately, the accessibility of CMR is limited in many thalassemia care centers, and patients often need to be referred to other centers for proper evaluation, resulting in inadequate patient follow-up [5, 6].

Aims and objectives

The objective of this study conducted at a tertiary care hospital in India was to examine the development and progression of electrocardiographic abnormalities and arrhythmias in patients with thalassemia major (TM) over a duration of 12 months. The study aimed to assess any changes or trends in the ECG patterns and arrhythmias observed in TM patients during this time period.

MATERIALS AND METHODS

This prospective study included 25 individuals diagnosed with thalassemia major (TM) who had a history of blood transfusions and were referred to the facility for cardiac function evaluation. These participants were either experiencing palpitations or undergoing cardiac assessment for other reasons. Individuals who did not have a normal sinus rhythm or exhibited evident cardiac conditions such as reduced ejection fraction, valvular heart disease, or pulmonary arterial hypertension were excluded from the study. To be eligible for participation, individuals must have received a blood transfusion within the week prior to enrollment.

To gather data on the participants' cardiac activity, all individuals underwent 24-hour electrocardiography (ECG) Holter monitoring. The recordings obtained during this period were meticulously analyzed, with a focus on identifying the different types of beats, including normal and ectopic beats, as well as identifying any noise or artifacts present in the recordings. In addition to the standard electrocardiographic measures, the study also examined specific characteristics related to heart rate variability (HRV) and thoroughly analyzed any episodes of arrhythmias observed during the monitoring period.

Statistical Analysis

In this study, if the continuous variables did not follow a normal distribution, they were presented as mean $\pm$ standard deviation (SD) or as median with the 25th-75th percentile range [25th-75th percentile]. To assess normality, the Kolmogorov-Smirnov test was utilized. The comparison of continuous variables was performed using either the paired Student's t-test or the non-parametric Wilcoxon signed-rank test. Categorical variables, expressed as frequencies, were compared using McNemar's test. A two-tailed P value of 0.05 was considered statistically significant. For these statistical analyses, the SPSS program (version 21.0; SPSS) was used.

RESULTS

The study group consisted of 25 patients with thalassemia major (TM) who had a median age of 38 years (range: 34-45). Out of the total participants, 15 (60%) were males. All patients completed the 12-month follow-up, as well as the initial diagnostic assessments and tests. Apart from a notable improvement in estimated creatinine clearance, as

Table 1: Variation in clinical and echocardiographic features in the population investigated

Thalassemia Patients (N = 25)	Baseline	12 Months	P-Value
BMI (kg/m2)	24.3±2	21.3±4	0.76
Hypertension, n (%)	2(8%)	2 (8%)	1
Diabetes, n (%)	3 (12%)	3 (12%)	1
Dyslipidemia, n (%)	0	0	1
History of paroxysmal AF	2 (8%)	2(8%)	1
Current Smokers, n (%)	7(28%)	7 (28%)	1
*Systolic blood p*ressure (mmHg)	114±12	109±15	0.80
Hemoglobin (gr/dl)	9.9 [9-10.4]	10.2 [9.2-10.9]	0.79
Ferritin	1347 [760-1856]	1239 [720-1965]	*0.88*
Creatinine (mg/dl)	0.8	0.75	0.39
Creatinine clearance (ml/min)	88	98	0.01
LVEF (%)	*55*	54	0.76
LA diameter (mm)	34	*34*	0.88
LA volume (ml)	57	55	*0.61*
PASP (mmHg)	28	31	0.90

Abbreviations: AF: atrial fibrillation; BMI: body mass index; LA: left atrial; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure

Table 2: Variation in treadmill exercise stress test parameters in the study population

Thalassemia Patients (N = 25)	Baseline	12 Months	P-Value
Duration (min)	7.35 [5.57-9.01]	9.32 [7.2-10.1]	0.32
METs	8.9 [7.9-10.6]	10.2 [9.9-11.9]	0.46
HRR1	28 [20-33]	27 [17-32]	0.75
HRR2	56 [50-67]	61 [57-72]	0.59
HRR3	64 [62-66]	59 [60-65]	0.86
HRR6	73 [67-81]	68 [62-77]	0.77

shown in Table 1, the clinical and echocardiographic characteristics of the TM patients remained similar between the baseline and follow-up evaluations. Throughout the 12-month follow-up period, there were no significant changes observed in the electrocardiographic indicators of atrial and ventricular depolarization, as well as the markers of ventricular repolarization/repolarization heterogeneity.

The study found a significant increase in the number of supraventricular ectopic beats observed in the 24-hour Holter recordings. However, there was no significant difference in the detection of paroxysmal atrial fibrillation (PAF) between the baseline and 12-month follow-up assessments (1/25 at baseline vs. 1/25 at 12 months; P = 0.38). The average duration of PAF episodes was 61 minutes, and the average number of atrial fibrillation (AF) episodes was 91. It is worth noting that none of the patients were taking beta-blockers or any antiarrhythmic medication during the trial period. As none of the patients had a CHA2DS2VASc score greater than 1, no anticoagulant medication was recommended. Additionally, there were no substantial changes observed in the autonomic imbalance indexes measured during the 24-hour Holter recordings or in the recovery phase of the exercise test, as shown in Table 2.

DISCUSSION

During the 12-month period, we observed that the electrocardiographic (ECG) abnormalities and autonomic function issues in TM patients with preserved left ventricular ejection fraction (LVEF) did not progress significantly. However, there was a notable increase in the burden of supraventricular ectopic beats, and a higher number of patients were found to have paroxysmal atrial fibrillation (PAF) during the follow-up. Specifically, one-fourth of the patients exhibited PAF in the 24-hour Holter record-

ings, with approximately one-third of these episodes being asymptomatic. These findings suggest that longer and/or more frequent ECG monitoring could potentially improve the diagnostic yield in terms of detecting arrhythmias in TM patients [7, 8].

In this study, we examined various electrocardiographic indicators and arrhythmic events detected through Holter monitoring in a specific group of thalassemia major (TM) patients who did not have systolic heart failure [9]. Additionally, we conducted an analysis of the results from exercise stress testing in all participants, focusing on heart rate recovery as a novel indicator of autonomic dysfunction [10]. Although recent studies have explored ECG abnormalities and arrhythmic risk indices in TM patients, the observed ECG abnormalities did not demonstrate significant changes during the 12-month follow-up period [11, 12]. It is possible that the duration of the follow-up was too short to identify substantial alterations in the ECG abnormalities.

Iron-induced oxidative stress is known to cause cellular and cardiac damage, inflammation, ion channel dysregulation, and disturbances in calcium handling [13]. Regardless of the presence of cardiomyopathy, iron-related damage contributes to the development of arrhythmias [14, 15]. However, as myocardial function deteriorates, the burden of arrhythmias tends to increase.

CONCLUSION

In TM patients without evident heart failure, ECG repolarization abnormalities and autonomic function issues persist throughout a short follow-up period. Although a significant portion of these events may not exhibit symptoms, the severity and occurrence of supraventricular ectopic beats and atrial fibrillation (AF) appear to increase over a relatively short timeframe of 12 months. Therefore, close monitoring and detection of arrhythmias are crucial in this cohort. Longer follow-up studies with more comprehensive ECG monitoring are needed to provide a clearer understanding of the specific burden and prognostic impact of certain ECG and arrhythmic indicators in this context.

Conflict

Nil.

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Nil.

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