Original Article

Evaluation of myocardial perfusion and function in patients with asymptomatic beta-thalassemia major using myocardial gated single-photon-emission computed tomography

ABSTRACT

This study was conducted to evaluate the cardiac perfusion and function of patients with beta-thalassemia major (TM) using ^{99m}Tc-MIBI cardiac gated single-photon-emission computed tomography (SPECT) and to compare the obtained indices with echocardiographic and hematological parameters. Patients with TM who were referred for regular blood transfusion and periodic checkup were included in this study. A questionnaire containing demographic and medical data was provided for all patients by an expert pediatrician. All of the patients were on Desferal chelation therapy and none of them had clinical signs of heart failure. Myocardial gated perfusion SPECT, echocardiography, and complete blood tests were performed for each patient. In total, 24 patients including 14 men (58.3%) and 10 women (41.7%) aged 15–36 years with a mean age of 24.3 ± 6.5 years' old were enrolled in this study. Myocardial perfusion scan (MPS) was normal in all patients. The mean value of the measured left ventricular ejection fraction (LVEF) was 58.88 ± 13.45%. There was no significant association between measured LVEF on scan and echocardiography ($P > 0.05$). In terms of hematological results, there was a significant association between the hemoglobin and ferritin level and the amount of blood transfusion ($P = 0.02$ and $P = 0.00$, respectively). According to the results of myocardial perfusion imaging (MPI), cardiac perfusion and LVEF were within normal limits in all asymptomatic patients. In the absence of any perfusion abnormality, the use of MPI in patients with asymptomatic beta-TM is not recommended for diagnosing myocardial ischemia.

Keywords: Beta-thalassemia major, cardiac single-photon-emission computed tomography, myocardial ischemia, myocardial perfusion imaging

INTRODUCTION

Beta-thalassemia, a hereditary blood disorder, is a chronic hemolytic anemia caused by impaired synthesis of the beta hemoglobin (Hb) chain resulting in an intense decline in the red blood cell life span leading to variable phenotypes ranging from severely anemic to clinically asymptomatic individuals.[1] There are three types of thalassemia, including thalassemia major (TM), thalassemia intermedia, and thalassemia minor. TM is usually diagnosed within the first 2 years of life with severe anemia.[1]

After diagnosing TM, regular blood transfusion and chelation treatment are very important for survival. However, these transfusions lead to siderosis in the myocardium and cardiac dysfunction would develop depending on the frequency and duration of transfusions.[2] The iron deposition in the heart is the main cause of morbidity and mortality in TM patients.

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Studies have found a relationship between the development of cardiovascular complications and elevated iron levels.[3] Iron, which is an important part of several enzymes, becomes very cytotoxic when excess amounts are deposited in the tissues of TM patients due to repeated blood transfusions.[4] Iron-induced cardiac dysfunction manifests as congestive heart failure (CHF), different arrhythmias, and regional wall motion abnormalities. Moreover, excess iron may accelerate lipid peroxidation due to pro-oxidant properties causing early atherogenesis.[3] Iron-induced CHF is the most prevalent cause of mortality in these patients.

Early diagnosis of beta-thalassemia may lead to fast chelation therapy resulting in a finer life. Since iron accumulates in the myocardium, biopsy is the most accurate procedure for beta-thalassemia diagnosis, but since it is an invasive technique, it is not usually preferred clinically. In these patients, the cardiac function is evaluated using noninvasive techniques such as magnetic resonance imaging (MRI), computed tomography (CT) scan, and echocardiography. A recent study investigated various conventional echocardiography parameters to evaluate cardiac function in patients with asymptomatic thalassemia.[5] Cardiac dysfunction is associated with a poor prognosis because echocardiography parameters are normal until cardiac dysfunction is clinically manifest.[6,7] New echocardiographic techniques such as tissue Doppler imaging (TDI) can be used to evaluate cardiac function and to monitor and identify subclinical heart failure.[8,9] T_2^* cardiovascular MRI is the best method for screening cardiac iron load. It can identify cardiac iron overload before cardiac dysfunction occurs; therefore, management strategies can be implemented instantly. However, this method is expensive and unavailable in many regions.[10]

It has been shown that stress radionuclide ventriculography (RNV) can be used to detect functional abnormalities in thalassemia patients during exercise before they become apparent at rest.[11] Furthermore, studies have revealed that some cardiac failures in TM patients, such as regional wall motion abnormalities that frequently occur in the septum as early damage, can be detected by ^{99m}TC-tetrofosmin myocardial perfusion scintigraphy.[4,12] Since heart failure and its extent can be detected with cardiac gated single-photon-emission CT (SPECT), this study was conducted to evaluate cardiac perfusion and function in TM patients using ^{99m}TC-MIBI cardiac gated SPECT.

MATERIALS AND METHODS

Study population

TM patients who had regular blood transfusions and periodic checkups with a negative history coronary artery disease (CAD) or cardiac symptoms were included in this study. Inclusion criteria were a definitive diagnosis of TM by Hb electrophoresis and confirmation of the TM diagnosis by hematological tests available in the patient's medical records. Exclusion criteria were a history of acute coronary syndrome, myocardial ischemia, previous myocardial infarction, and cardiomyopathy. Patients with insufficient data were also excluded from the study.

CAD was evaluated using myocardial perfusion imaging (MPI)–gated SPECT imaging in the nuclear medicine department of a university affiliated hospital. MPI results were compared with the obtained paraclinical data.

A questionnaire containing demographic and medical data was provided for all patients by an expert pediatrician. All of them were on Desferal chelation therapy and none of the patients had clinical signs of heart failure. The study protocol was explained to patients and their parents and informed consent was obtained from them. This study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Bushehr University of Medical Sciences (registration code: IR.BPUMS.REC.1396.26/ date: June 19, 2017).

Single-photon-emission computed tomography acquisition protocol

On the same day, a stress-rest protocol was used for gated MPI acquisition. Pharmacologic stress was induced through intravenous injection of 0.56 mg/kg dipyridamole over 4 min. ^{99m}Tc-sestamibi at a dose of about 20 mCi was injected intravenously for each phase and SPECT was performed after at least 60 min in the supine position with a dual-head scintillation camera (Vertex-Plus, ADAC Laboratories, Silicon Valley, USA) equipped with a low-energy high-resolution collimator. Thirty-two projections (20 s/projection) were obtained using step-and-shoot acquisition method in the 90° setting (from 45° right anterior oblique to 45° left anterior oblique), and also, gated in the rest phase was obtained with an R-wave trigger at eight frames per cardiac cycle and stored in a 64 × 64 matrix. No attenuation correction was used in the processing. Image reconstruction was done using the filtered back-projection method by Butterworth filters with a cutoff of 0.45 and order of 9.0. The raw data were reconstructed for all projections by an experienced technologist in nuclear cardiology. An experienced nuclear medicine specialist supervised the cardiac SPECT protocol.

All images were interpreted visually by two experienced practitioners who reached consensus on findings. The nuclear medicine specialists were blind to the data of the cases.

Echocardiography protocol

A Samsung echocardiography machine with a 3.5 MHz transducer was used for electrocardiography. The patients were positioned in left lateral decubitus at rest and parasternal long-axis and short-axis and apical two- and four-chambers views were obtained. The lower limit of normal left ventricular ejection fraction (LVEF) was considered 50%. Visual scores were used for regional wall motion of the LV myocardium according to the following scale: normal = 0; mild hypokinesia = 1; moderate hypokinesia = 2; severe hypokinesia = 3; and dyskinetic = 4. Moreover, ejection fraction, end-systolic cavity dimensions, and left ventricular end-diastolic volume were measured. Furthermore, pulmonary arterial pressure (PAP) was measured in some patients.

Blood measurements

Laboratory data including low-density lipoprotein, high-density lipoprotein, cholesterol, triglyceride, alanine transaminase (ALT), aspartate aminotransferase (AST), Hb, ferritin, and the amount of blood transfusion during a year were extracted from patients' medical records.

Statistical analysis

Quantitative data were presented as the mean ± standard deviation with ranges given when appropriate. Qualitative data were expressed as percentage. Chi-square was used to analyze qualitative variables. SPSS Statistics 21 (IBM Corporation, Somers, NY, USA) was used for the statistical analysis. $P < 0.05$ was considered significant.

RESULTS

Demographic data

In total, 24 patients including 14 men (58.3%) and 10 women (41.7%) aged 15–36 years with a mean age of 24.3 ± 6.5 years' old were enrolled. Splenectomy had been performed in 14 patients (58.3%) and all of them were on Desferal chelation therapy [Table 1].

Hematologic data

The mean amount of blood transfusion during a year was 7435.23 ± 3802.75 cc, and mean Hb level was 8.17 ± 0.57 g/dL (from 7 to 9.1 g/dL), and the mean ferritin level was 2374.75 ± 2033.19 ng/ml (from 300 to 7820 ng/ml). Other laboratory parameters are presented in Table 1.

Echocardiography data

According to the results of echocardiography, the mean LVEF was 54.45% ± 6.18% in the patients. The mean PAP measured was 29.12 ± 6.24 mmHg in eight patients. Diastolic dysfunction was observed in all of the patients.

Table 1: Statistical description of data

	Minimum	Maximum	Mean±SD
Age (years)	15.00	36.00	24.3333±6.55854
BT (cc)	330.00	14520.00	7435.2381±3802.75376
Ferritin (ng/mL)	300.00	7820.00	2374.7500±2033.19719
TG (mg/dL)	109.00	313.00	164.7500±49.39746
Cholesterol (mg/dL)	79.00	202.00	126.5417±33.09667
LDL (mg/dL)	34.00	99.00	64.8750±15.13795
HDL (mg/Dl)	15.00	57.00	36.1250±11.61451
ALT (IU/L)	10.00	81.00	26.7917±18.08910
Hb (g/dL)	7.00	9.10	8.1708±0.57217
ECHEF (%)	38.00	65.00	54.4583±6.18539
PAP (mmHg)	20.00	35.00	29.1250±6.24357
SCANEF (%)	42.00	82.00	58.8889±13.45775
SCANEDV (ml)	42.00	188.00	85.2222±44.17516
SCANTID	0.68	1.09	0.9433±0.13304
SCANLHR	0.13	0.43	0.3363±0.09070

BT: Blood transfusion; ECHEF: Ejection fraction of echocardiography; PAP: Pulmonary arterial pressure; SCANEF: Ejection fraction of scan; SCANEDV: End-diastolic volume of scan; SCANTID: Transient ischemic dilatation of scan, SCANLHR: Lung-to-heart uptake ratios of scan; SD: Standard deviation; ALT: Alanine transaminase; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Hb: Hemoglobin

Cardiac gated single-photon-emission computed tomography

Myocardial perfusion scan (MPS) was normal in all patients. The mean LVEF was 58.88% ± 13.45%. Moreover, the mean end-diastolic volume, transient ischemic dilation, and lung-to-heart uptake ratio was 85.22 ± 44.17 ml, 0.94 ± 0.13, and 0.33 ± 0.09, respectively.

Data analysis

There was no significant association between measured LVEF on scan and echocardiography ($P > 0.05$). In terms of hematological results, there was a significant association between the Hb and ferritin level and the amount of blood transfusion ($P = 0.02$ and $P = 0.00$, respectively). In addition, there was no significant association between the level of ALT and the amount of blood transfusion ($P > 0.05$) and between the level of ferritin ($P > 0.05$) and the level of AST ($P > 0.05$).

DISCUSSION

Patients with TM suffer from serious chronic anemia and iron overload due to regular blood transfusions. Clinical manifestations of iron overload, including hypogonadism (35%–55%), hypothyroidism (9%–11%), hypoparathyroidism (4%), diabetes (6%–10%), liver fibrosis, and cardiac dysfunction (33%), develop in TM patients maintained on a regular transfusion regimen.[1] In these patients, cardiac dysfunction is the main clinical problem and a leading cause of mortality, especially in the second decade.[13] Considering that myocardial hemochromatosis may develop without clinical manifestations,[14] a noninvasive procedure that can

detect cardiac dysfunction in early stages is very helpful in these patients. Although rest echocardiography can identify functional and anatomical abnormalities in some patients prior to the onset of clinical manifestations, the majority of the patients without clinical CHF do not show conclusive echocardiographic evidence at rest.[15] T_2^*MRI is the best screening modality and can detect cardiac iron overload before the development of cardiac failure. Nevertheless, this method is expensive and is not available in many centers.[9]

In this study, cardiac gated SPECT was used to evaluate cardiac dysfunction in asymptomatic patients with TM. None of the patients had signs of cardiac problems. MPS was within the normal range in all of the patients. Moreover, LVEF obtained from gated SPECT was in the normal range. Few studies have investigated the value of MPS in cardiac assessment of patients with TM. Gedik *et al*.[4] found regional cardiac wall motion abnormalities in TM patients. This early injury is mostly located in the septum and can be identified with MPS. In another study, Küçük *et al*.[2] evaluated myocardial perfusion using thallium scan and left ventricular function using rest RNV. The results showed that in TM patients, ischemia and fixed defects might be observed in stress MPS as a result of heart involvement. However, RNV was preferred for the early detection of subclinical cardiomyopathy. In another study, exercise MPS was used to determinate the mechanism of myocardial ischemia in sickle beta-thalassemia patients. It was found that physical stress might lead to myocardial ischemia in patients with normal coronary arteries and elicit painful crises.[12] All of the patients in the present study had major thalassemia and none of them had a sickle cell-related allele. Moreover, perfusion defects or ST depression were not observed on electrocardiogram during the stress phase of the study. Therefore, the existence of sickle cell-related allele in sickle beta-thalassemia patients is a predisposing factor for myocardial ischemia and painful crises during physical stress.

According to the results of echocardiography, although LVEF was in the normal range in all patients, all of them suffered from diastolic dysfunction. In one study, systolic and diastolic functions of the left ventricle were assessed using TDI and it was found that diastolic indices of the LV showed higher early diastolic filling of LV and E/A ratio suggesting a restrictive diastolic pattern and stiff myocardial wall in the patients.[16] Similarly, Yaprak *et al*.[17] found that patients had a significantly higher E-wave and lower A-wave and E/A ratio velocity indicating a restrictive pattern while no correlation was found with the Hb level.

This study had some limitations. The most important limitation was its small sample size, which may necessitate further investigation. Moreover, the association between possible perfusion abnormalities and cardiac iron overload should be investigated in future studies using state-of-the-art technologies like positron-emission tomography-MRI. In addition, for a more accurate assessment of diastolic dysfunction in cardiac gated SPECT for comparison with echocardiography, it is better to use 16 frames per cardiac cycle instead of 8 frames per cardiac cycle,[18] but it was not done in the present study.

CONCLUSION

According to the results of MPI, cardiac perfusion and LVEF were within normal limits in all asymptomatic patients. In the absence of any perfusion abnormality, the use of MPI in patients with asymptomatic beta-TM is not recommended for diagnosing myocardial ischemia.

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Conflicts of interest

There are no conflicts of interest.

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