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Prevalence of Heart Failure in the Cases of Beta-thalassemia Major; Two Years Follow-Up

Atooshe Rohani[1], Vahid Akbari[2], Mehdi Moradipoor[3], Mehdi Akbartabar[3]

[1] Cardiologist, ardiac Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Cardiologist, 17 Shahrivar Haspital,Mashhad,Iran
[3] Cardiologist, Yasuj University of Medical Sciences, Yasuj, Iran

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ABSTRACT

Inroduction: Heart failure (HF) is an important cause of morbidity and mortality in the cases of Beta-thalassemia major. The purpose of this study was to estimate HF prevalence in these patients and to assess the survivability of those who were treated with intensive chelating therapy.
Design and methods: This cross sectional study included 72 beta-thalassemia major cases, the mean age at the time of referral was 15.7±6.2 years (range 6-35 years) and were followed in a prospective 2 year study. A self-reporting symptom questionnaire was administered, a 12-lead ECG was taken and an echocardiography was obtained from all participants. Echocardiography was performed at 6 month intervals or when a new symptom developed.
Results: Risk factors (except for iron overload) in the study population were hypothyroidism and diabetes mellitus. The male to female ratio was0.75.Twelve patients had left ventricular (LV) systolic dysfunction and 57,79% had LV diastolic dysfunction whereas 11,15% had RV failure. Fifty-nine (81%) patients had cardiac disease of which diastolic dysfunction was the most common manifestation .Those with systolic dysfunction were older at presentation (22 ± 6 years versus 31 ± 4 years; P <0.001), and had the highest mean serum ferritin level (3,355 ± 1241 ng/mL versus 6,397 ± 1,613 ng/mL; P <0.001). The 2 year survival rate in patients with beta thalassemia in this study was 98%.
Conclusions: Diastolic dysfunction is highly prevalent in even asymptomatic beta-thalassemia major patients. The high prevalence of diastolic dysfunction is indicative of a significant amount of the population who are at a high risk for HF.

Introduction

Beta-thalassemia major is the most common hemolytic anemia in children and adolescents, particularly in Iran. In patients with thalassemia major, cardiac abnormalities are important causes of morbidity and mortality and are the major cause of death in these patients. Even with the best medical care, one third dies by the age of 35 (1). When cardiac dysfunction occurs in these patients, it is generally due to iron overload, and in some cases it may be caused by viral myocarditis (2). Myocarditis can cause acute or chronic left ventricular systolic dysfunction and dilatation, which appear to be mediated by predominantly immunologic mechanisms rather than viral infection and replication (3,4). Thalassemia major patients differ from healthy individuals in that they tend to be younger and generally have lower systemic needs therefore conventional echocardiographic indices that are routinely applied for the estimation of adult cardiac function face a number of limitations thereafter we used Tei index (5). Thalassemia represents a chronic, high-output state produced by volume-loaded ventricles rather than increased heart rates. These patients present higher values of EF if related to normal population.The purpose of this study was to estimate HF prevalence in these patients who were referred for annual screening and to evaluate whether intensive chelation therapy improved the odds of their survival.

* *Corresponding author:* Atoosheh Rohani, Cardiac Research Center, Mashhad University of Medical Sciences, Mashhad, Iran , *E-mail:* RohaniA@mums.ac.ir, Tel:05118012806 fax:05118402972

Meterials and Method

Seventy two consecutive patients with beta thalassemia major were followed in a prospective 2 year study. The study was approved in the ethical committee of Yasuj university of medical sciences. These patients were referred to Yasuj Mofatteh clinic by their family physicians for routine annual screening. Asymptomatic thalassemia cases were included. Exclusion criteria were congenital heart disease, patients who were not in sinus rhythm and patients with pacemakers or bundle branch block, high grade atrioventricular block or severe heart valve disease. All subjects underwent intensification of chelation therapy with deferrioxamine with five-days-a week via subcutaneous infusion. Those with systolic dysfunction were prescribed angiotensin converting enzyme (ACE) inhibitor (either captopril or enalapril) and if they had sign of congestion, diuretics (furosemide and spironolactone, alone or in combination) were prescribed. Those with symptomatic diastolic dysfunction received beta-blockers (metoprolol or carvedilol). Clinical history included age at diagnosis, blood transfusions frequency and conjunctive chelation therapy. Cardiovascular investigations included electrocardiogram and echocardiogram. Echocardiographic examination images were taken in the left lateral decubitus position with an echocardiography machine (Esaote Biomedica, Florence, Italy) with a 5 MHz transducer for children and 3.75 MHz for adult. The frequency of echocardiographic performance throughout the follow-up in asymptomatic patients was every 6 months and in symptomatic was individualized according to severity of the disease. An electrocardiogram was simultaneously recorded for each patient. The echocardiographic examination was done using standard views and techniques according guidelines of the American Society of Echocardiography (4).Left ventricular ejection fraction was measured by the Simpson method. Global systolic function was considered abnormal if the ejection fraction was less than 55%. For recordings of the mitral inflow velocity pattern, the sample volume 2 mm in size of the pulsed doppler has been placed between the tips of the mitral leaflets in the apical four-chamber view (5,6,7). Accordingly, the left ventricular outflow velocity was recorded from the apical long-axis view with the sample volume of the pulsed doppler positioned just below the aortic annulus. Left ventricular diastolic function was defined by the pattern of transmitral inflow on spectral doppler interrogation, consisting of E/A ratio, E wave deceleration time and isovolumetric relaxation time (5). Diastolic dysfunction (grade 1) (5,6) was diagnosed when the E/A ratio was less than 1, deceleration time was more than 220 ms in adults and 180 ms in children, or the isovolumetric relaxation time more than 65 ms in adults or 55 ms or more in children. Restrictive left ventricular function (grade 2) was diagnosed when the E/A ratio calculated more than 2.5 and the deceleration time of E wave less than 160 millisecond (5). Myocardial performance index, "the Tei index", was calculated by dividing the sum of isovolumetric contraction and relaxation times by the left ventricular ejection time (7,8,10,11), and this indicated the combined systolic and diastolic function of the myocardium. The Tei index was considered abnormal if it was more than 0.46 (normal 0.38 ± 0.7 in children and 0.41 ± 0.05 in adults) in the left ventricle (7,8). The non-invasive estimate of pulmonary arterial pressures indicated by systolic pressure gradient across the tricuspid valve. Pulmonary hypertension was diagnosed if the peak systolic pressure gradient at the tricuspid valve was more than 30 mmHg. About 3 ml of patient's blood sample was collected by a venepuncture and Ferritin levels were measured by ELISA .If it is greater than 300 ng/ml may indicate increased iron stores.Intra-observer variability was assessed in 10 patients by repeating the measurements on two occasions (1–12 days apart) under the same basal conditions. To test the inter-observer variability, the measurements were performed off-line from video recordings by a second observer who was unaware of the results of the first examination. Variability was calculated as the mean percentage error, derived as the difference between the two sets of measurements, divided by the mean of the observations. Data are expressed as mean value ± SD. Variables derived from echo doppler measurements were compared by an unpaired student's t-test, if appropriate, or a Mann–Whitney. Statistical analysis was done using the SPSS version 17.0 (Chicago, IL, USA) and a difference was considered significant at $P<0.05$.

Results

Patients hematologic and echocardiographic data are given in table 1 and 2. There were 31 males and 41 females. The mean age at the time of referral was 15.7 ± 6.2 years (with the range 6-35 years). Blood transfusion was started at a mean age of 1.1 ± 1.5 years. Transfusion was repeated at a mean of 20.4±10.9 days (range of 3-90 days). Mean blood pressure was measured 90/60±8/9 and mean heart rate was documented as 75±8. At the initiation of the study, chelation therapy with subcutaneous desferrioxamine therapy was practiced by 58 (80%) patients five nights per week. Symptoms such as orthopnea were present in 7 (9%) patients defined by NYHA(New York Heart Association Functional Classification) functional class ≥ 2 (mean 2.5±0.5). Extra cardiac evidence of iron overload was seen as hypocalcaemia, hypothyroidism and diabetes mellitus in 4patients (5%) and Tei-index ranged from 0.15 to 1.42. The index was significantly higher in symptomatic subjects than in asymptomatic ones (0.42±0.05 versus 0.68±0.1, P=0.01) and increased in newly symptomatic patients (mean 0.31±0.05) at the start of study versus 0.72±0.1, P=0.01 at the time of presentation of

Table 1. Hematologic Data

Variables	Systolic dysfunction	Diastolic dysfunction	RV failure
Mean hemoglobin, g/dL	8.7 ± 0.4	8.2 ± 1.2	8.4 ± 1.2
Mean serum ferritin, ng/mL†	2,815 ± 804	2,270 ± 918	2,470 ± 900
Peak serum ferritin, ng/mL†	3,876 ± 2,770	2,276 ± 1,125	3,175 ± 1,024
Splenectomy	5	30	2

Table 2. Echocardiographical Features in Patients Evaluated for Cardiovascular Disease.

Parameter	Number	(%) of patients
Normal echocardiogram	13	18%
Ejection fraction(<55%)	12	16%
Deceleration time>200 ms	3	4%
Deceleration time<160 ms	54	75%
Tei index >0.46	19	26%
TR* ≥40 mmHg	11	15%
Pericardial effusion	1	1.3%
Mild MR**	3	4%
Mild AI***	1	1.3%
LVH****	1	1.3%

TR*:Tricuspid Regurgitation, MR**: Mitral Regurgitation
AI***: Aortic Insufficiency, LVH****: Left Ventricular Hypertrophy

symptoms. Fifty-nine (81%) patients had cardiac disease of which diastolic dysfunction was the most common manifestation. Eleven patients (15%) had a peak systolic pressure gradient across the tricuspid valve of more than 40 mmHg. Out of this group, six had pressures measuring more than 50 mmHg, reflecting significant pulmonary arterial hypertension. This group of patients had abnormal Tei index which in men was significantly more than women (P<0.05). Statistically significant differences were found in desferrioxamine therapy and Tei index. In the regular users of desferrioxamine (5 days a week, at the start of study), Tei index was lower than irregular one (P<0.05). Our findings did not reveal any relationship between age and Tei index. Of the 14 patients who did not have desferrioxamine therapy, 8 had abnormal Tei index (P=0.05), and 2 had abnormal ejection fraction. The 2 year survival and event free rate in patients with beta thalassemia in this study were reported as 98%.All seven patients, except for one, in functional class II at initial presentation are still alive and in a stable clinical condition following a mean follow-up of 18±7 months. In two of them with left-sided heart failure, symptoms disappeared after intensified desferrioxamine use. This was accompanied by doubling of their left ventricular ejection fraction over 18 to 24 months and their Tei index had reduced to mean 0.43±0.02. Over 18±7 months, among the 7 symptomatic patients, death occurred in 1 (1.3%) while he had right ventricular dysfunction and pulmonary hypertension (PA pressure=60) and EF=50% as well as Tei equal to 1.1 at the start of study. He was on poor chelation therapy with very high ferritin values and in autopsy he had evidence of perimyocarditis, the clinical course and the deterioration of ventricular systolic function (within 4 months his EF was 15% and tei calculated to1.43). Six out of 13 (46%) patients with systolic left ventricular dysfunction and 20 out of 54 (37%) patients with diastolic dysfunction improved with cardiac medication and intensified chelation therapy. Pulmonary hypertension improved in two out of 11 (18%). The remaining patients are surviving on medical therapy with controlled symptoms. Three patients became symptomatic in follow-up; all of them had an abnormal index at the beginning of the study. From these 3 patients, one had sudden-onset left ventricular systolic dysfunction, with "influenza-like" symptoms and appearance of ECG alterations as well as cardiac enzyme release in favor of myocarditis. He had a complicated course with recurrent hospital admissions, and unfortunately after 2 months he died.

Discussion

Iron-overload cardiac disease in patients with beta-thalassemia major is often fatal and unfortunately is a common complication of thalassaemia major. Desferrioxamine is the most effective and safest iron chelator for prevention and treatment of iron overload cardiomyopathy (9).

Diastolic left ventricular dysfunction develops early, but most patients die of systolic dysfunction. However, with regular chelation and anticongestive therapy, the systolic dysfunction was seen to improve. The Tei-index was easily obtained and highly reproducible. The index was significantly higher in subjects with symptoms than in asymptomatic cases. Our observations are in agreement with the findings of Tei *et al.* who studied patients with severe and intermediate dilated cardiomyopathy (10). In those patients, the index was significantly higher than healthy individuals and increased with worsening of systolic left ventricular function. Our results reveal that the index provides useful information even in asymptomatic patients who will become symptomatic in the future and

the index is a sensitive indicator of overall cardiac dysfunction in patients with thalassemia major. It has been shown that early recognition and intervention may alter outcomes (13,14). Our asymptomtic patients also had higher EF. In our series, 57 out of 72 (79%) patients had diastolic dysfunction and 13 (16%) had systolic dysfunction, whereas 57 out of 72 (79%) patients had a global heart problems. Predominant right heart failure has been attributed to pulmonary hypertension, which was postulated to occur secondary to lung haemochromatosis, largely in patients with high ferritin levels. According to a study in the UK, survival rate of beta-thalassaemia major was about 85% (17). Our patients' survival rates are better than this study. This may be due to intensive chelation treatment that has significantly reduced the incidence of myocardial dysfunction and has led to an increase in survival.Our study merits few limitations as assessment of adherence to chelation therapy may have been imprecise due to its subjective nature. Secondly, Myopericarditis (9), a reported cause of left heart failure in thalassaemic patients, was not investigated with endomyocardial biopsy or MRI in our patients and thirdly the nature of our study which was in short term follow-up.

Conflict of interest: none

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