



ORIGINAL ARTICLE

Cardiac Disorders in Children with B-Thalassemia Major

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ABSTRACT

Cardiac failure due to transfusional iron overload is the major cause of death in patients with β -thalassemia major. Also ineffective erythropoiesis and increased gastrointestinal iron absorption lead to iron overload in the body and this induced heart failure. For this reason, regular evaluation of cardiac function is recommended for all the patients as integral part of their management to identify early changes in the left ventricular function. The study was conducted in Qom Children's Hospital, Iran, from 1st March 2008 to 30th October 2012; of 140 confirmed cases of β thalassemia major and control group consisted of 50 healthy children. β thalassemia major patients were diagnosed on the basis of hemoglobin electrophoresis. 2-D, M-mode and Doppler echocardiography was performed in all study cases. Statistical comparison of study cases and controls was conducted by using unpaired t-test. The age of the patients ranged from 3 year to 22 years with mean age of 14.25 years. There were 86 (61%) males and 54 (39%) females. All the patients were on irregular chelation therapy 42 (33%) patients had LV dysfunction; global dysfunction. Left ventricular dimensions, stroke volume and E/A ratio were considerably affected in the study group. A significant percentage of thalassemia patients have left ventricular dysfunction. This is mainly due to chronic anemia, iron overload. Regular cardiac function monitoring may reduce the cardiac complication to a great extent.

Keywords: β -thalassemia, Anemia, Calcium channels

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INTRODUCTION

Beta (β)-thalassemia major is the most common hemolytic anemia in children and adolescents, [1]. Thalassemia patients have extra vascular hemolysis and ineffective erythropoiesis, so, they require regular blood transfusions, which results in iron overload; receive between 0.3 and 0.5 mg/kg/d of iron through transfusion [2]. Overload iron deposit in heart, liver, gonads, and pancreas. In heart, the iron leads to impaired function of the mitochondrial respiratory chain, which is clinically manifested by the reduction of cardiac contractility, progressive systolic dysfunction, and development of heart failure [3]. Also calcium channels of the sarcoplasmic reticulum, which modulates calcium release, is disturbed, resulting in further reduction of cardiac function, conduction problems, and arrhythmia development [4]. So, if the iron not chelated, due to cardiac dysfunction, a third of patients die by the age of 35 years [2]. Despite adequate chelation, cardiac pathology is still present due to a combination of factors such as iron deposition, fibrosis, hypertrophy and structural effects of chronic anemia [3]. In fact, cardiac disease is responsible for 70% of deaths in thalassemia major patients [5], mostly presented as congestive heart failure [6]. Early detection of cardiac involvement and aggressive chelating therapy can reverse the condition [7]. Echocardiography of left ventricular structure and performance is suit for cardiac evaluation [8]. Chronic anemia is responsible for an increase in cardiac output, results from decreased systemic vascular resistance due to decreased blood viscosity and vasodilatation [9].

The enhanced left ventricular performance observed in anemia has been attributed to changes in pre-load and after-load. Chronic anemia also causes cardiac dilatation and hypertrophy [10]. We studied 140 β -thalassemia major patients in order to determine the effects of chronic anemia and transfusion iron overload on the left ventricular function by Doppler echocardiography. We believe that early detection and treatment of cardiac function impairment can assist in preventing further cardiac damage.

METHODS AND MATERIALS

It was an observational cross-sectional study from 1st March 2008 to 30th October 2012, Qom Children's Hospital, Iran. Written informed consent was obtained from all the patients and their parents. The study comprised of 140 cases of β -thalassemia major diagnosed based on hemoglobin electrophoresis findings. Patients with any congenital or acquired heart disease, concurrent infective disorder and patients with history of any type of cardiac surgery were excluded from the study. The control group consisted of 50 healthy children comparable in age and sex. Clinical examination done and hemoglobin, chest X-ray, electrocardiogram and serum ferritin levels were obtained in all the patients. Echocardiography (Two dimensional, M-mode and Doppler echocardiographic assessment) was performed in the thalassemia and the control group; using phased array sector scanner with 5 MHz transducers, Vivid 3 Echo machine; in the parasternal long axis and short axis and apical four chamber views were obtained in all the cases

Echocardiographic Measurements

The left ventricular end systolic and end diastolic dimensions, left ventricular posterior wall thickness, fractional shortening (FS%) and septal thickness, were measured by M-mode according to the recommendations of the American Society of Echocardiography (ASE). The left ventricular ejection fraction percentage (EF%) and stroke volume were calculated by using Simpson's method. To record left ventricular inflow velocities the apical four chamber view was used and the pulsed-wave Doppler sample volume was placed at the level of the leaflets tips of the mitral valve, where the highest peak velocity was recorded. Peak flow velocities of the left ventricle inflow in early diastole (E) and late diastole with atrial contraction (A) were measured from the baseline to the maximum flow velocity. An E/A velocity ratio, deceleration time (DT) and isovolumetric relaxation time (IVRT) were calculated from each cardiac cycle. Systolic function was considered abnormal if the EF was less than 55% and the FS was below 27%. 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. Diastolic function was classified according to the published ASE guidelines into normal, abnormal relaxation pattern (mild), the intermediate or pseudonormal pattern (moderate) and restrictive physiology (severe) pattern. Diastolic dysfunction was diagnosed as abnormal relaxation pattern (mild) when the E/A ratio was less than normal, deceleration time and the isovolumetric relaxation time were more than expected normal for that particular age group and pseudonormal when E/A ratio was in normal range, but on valsalva maneuver E/A dropped to less than normal or there was associated significant systolic dysfunction. Restrictive left ventricular function was labeled when E/A ratio was more than normal, deceleration time of E-wave and isovolumetric relaxation time were less than expected normal. Following were the cut-off values of mitral inflow velocities, deceleration time and isovolumetric relaxation time used for diastolic dysfunction categorization according to different age groups [9] (measurement taken from ASE z-scoring).

RESULTS

In the study cases, the median age was 3 year to 22years with mean age of 14.25 years. There were 86 (61%) males and 54 (39%) females, on regular five nights per week chelation therapy with subcutaneous or oral desferrioxamine. Blood transfusion was started at a mean age of 1.2 ± 1.3 years. Transfusion frequency was at a mean of 21.0 ± 9.0 days. 42 (33%) patients had left ventricular dysfunction, out of which 7 (17%) patients had isolated systolic dysfunction, 25 (60%) had isolated diastolic dysfunction and 10 (23%) had global ventricular dysfunction.

15 (11%) patients had splenectomy. Mean pre-transfusion hemoglobin was 7.1 ± 1.12 g/dl in the study cases. Serum ferritin level more than 5000 ng/ml was present in 38 (27%) cases while the mean serum ferritin level for the whole study group was 3124 ± 1022 ng/ml. On chest X-ray, cardiomegaly was detected in 78 (56%) cases, while electrocardiograms of all the patients revealed regular sinus rhythm.

DISCUSSION

In this study, we found that interventricular septal thickness, LV posterior wall thickness, LV dimensions both in systole and diastole, fractional shortening, ejection fraction, stroke volume, E-wave, A-wave and E/A ratio were significantly higher in the study cases as compared to controls while the difference between deceleration time and isovolumetric relaxation time was not statistically significant. On echocardiography, β -thalassemia patients had cardiac enlargement with high stroke volume.

Our findings are generally consistent with previously reported findings in literature. Bosi *et al*, Chotivittayatarakorn *et al*, Kremastinos *et al* and Aessopos *et al* reported that the left ventricular diameter in thalassemic patients were significantly higher than in controls [11, 12]. The failure to detect impaired ventricular systolic function is not surprising since the hemodynamic effects associated with

anemia helped to maintain normal ejection fraction and myocardial fiber shortening. Atiq M *et al* reported that 23% of their study patients had LV systolic while 29% had diastolic dysfunction [13]. LV systolic dysfunction in 23% of patients is a higher percentage than our finding but their study comprised of those thalassemia patients who clinically had some symptoms and were actually referred for cardiac evaluation. Aldouri MA *et al* demonstrated that the interventricular septal thickness and left ventricular posterior wall thickness of the thalassemic cases was significantly increased compared to the control group ($p < 0.001$) which is in concordance with present study [8]. Bosi G *et al* and Spiritio *et al* reported that peak flow velocity in early diastole was increased in patients compared with controls and the ratio between the early and late (atrial) peaks of flow velocity were also increased [11, 14]. On the other hand, Kremastinos *et al* demonstrated an altered diastolic function by an increase of both early and late peak transmitral flow velocity without change of the E/A ratio, although 8% of their study patients had restrictive LV abnormalities [15]. In our study, we found an increase in both early and late peak transmitral flow velocities. An increase in E/A ratio along with shortened deceleration time (DT) and isovolumetric relaxation time (IVRT) was found in 28 (20%) of patients, reflecting a high percentage of restrictive physiology in our setup. However, Favilli S *et al* found that there was no difference between patients with thalassemia major and controls for Doppler diastolic indexes obtained from analysis of transmitral flow, which is not consistent with our finding [16]. Taksande A *et al* described that although there is an increase in LV dimensions and LV mass but LV diastolic function is not altered in asymptomatic patients [17]. In contrast, we found 33% of our asymptomatic patients had diastolic dysfunction. Vaccari M *et al* also concluded an increased E/A ratio in thalassemia major patients which is comparable with our study [18].

The pathophysiology of cardiomyopathy in β -thalassemia major is related to heart failure secondary to anemia, iron overload cardiomyopathy, acute infectious myocarditis, acute pericarditis, conduction abnormalities or right heart failure due to pulmonary hemosiderosis, alone or in combination [19] and cardiac dysfunction remains the leading cause of death [4]. All patients in our study had elevated serum ferritin. Iron overload in β -thalassemia major is the outcome of excessive absorption and transfusional hemosiderosis. The plasma turnover is 10-15 times of the normal value and is caused by the wasteful, ineffective erythropoiesis of an enormously expanded bone marrow. The resulting outpouring of catabolic iron exceeds the iron-binding capacity of transferrin and appears as non-transferrin plasma iron (NTPI).

NTPI is highly toxic due its ability to promote free radical formation through the Haber-Weiss reaction, resulting in peroxidative damage to membrane lipids and proteins [3]. The process of liberating of lysosomal enzymes, damages the cytoplasm of myocytes, impairs the Na/Ca exchange mechanism, resulting in cell death in the iron-overloaded heart [20]. Finally, iron overload causes injury to the mitochondria, leading to a decrease in the mitochondrial respiratory complex activity [21].

The relationship of total body iron overload to iron deposition within the myocytes and the development of myocardial dysfunction remains perplexing, because some patients with advanced hemosiderosis of other organs have little myocardial deposition [11]. In one study, conduction abnormalities correlated poorly with conduction tissue infiltration seen at autopsy in patients who died of arrhythmias [22]. Moreover, iron may cause reactive fibrosis or hypertrophy within the myocardium to account for the variable responses observed [12]. Vogel *et al* hypothesized that iron deposition is predominantly in the interventricular septum in the early stages [23]. Iron deposition is mainly within the ventricles and can be patchy [13]. Pathophysiologically, iron overload manifests as left ventricular diastolic dysfunction. However, as the disease progresses, systolic function also becomes impaired [24]. Aggressive chelation therapy may improve prognosis and should not be delayed until the development of overt heart failure [15]. Modell *et al* reported a marked improvement in survival and reduction in deaths due to cardiac iron overload in β -thalassemia major by early identification of myocardial siderosis by cardiac magnetic resonance imaging and appropriate intensification of iron chelation treatment [24]. Therefore, early recognition of cardiac abnormalities is essential in these patients, but not easy as global ventricular function and exercise capacity may remain normal until late in the disease process [16].

Co-operation of the treating physician with the cardiologist is necessary to establish the best treatment protocols. Echocardiography is an investigation that is widely available, relatively inexpensive, and easy to perform [21]. This is a simple, non-invasive way of recording early cardiac alterations in thalassemia major patients and enables long-term monitoring of cardiac function in the assessment of the effectiveness of the chelation therapy [22].

To conclude, we found the results that are consistent with previous studies for LV dimensions and systolic dysfunction but we found a higher percentage of diastolic dysfunction in our study. We believe that this higher percentage is most likely due to poor compliance with chelation therapy and non-availability of proper cardiac monitoring. Monitoring cardiac function can be a useful index to the overall

prognosis of a patient. The demonstration of impaired myocardial function might not only serve to alert the clinicians to start cardiac treatment, but it would also alert them to warn the individual patient that a much stricter adherence to chelation protocol or the initiation of a more intensive chelation program is required to prevent an inexorable progression to severe cardiac failure. Assessment of cardiac function by echocardiography on regular basis is a useful tool for this purpose.

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