CLINICAL STUDY

Risk Factors Linked to Development of Cardiomyopathy in Adults with Beta-Thalassemia Major in a Tertiary Care Hospital

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ABSTRACT

Beta-thalassemia major is a genetic disorder adversely affecting the life of the patient and the whole family. Repeated blood transfusions are required to maintain the hemoglobin level, which create a state of iron overload in the body leading to ectopic iron deposition in the heart, liver, pancreas and other organs. Thalassemia cardiomyopathy is the most dreaded complication of this resultant iron overload. The present study was a cross-sectional study involving 77 patients with thalassemia major, whose age, body mass index (BMI), blood pressure (BP), hemoglobin, serum ferritin levels were correlated with their two-dimensional echocardiographic findings. Out of the total 77 patients, 63 had diastolic dysfunction, 6 had systolic dysfunction and remaining 8 had normal left ventricular function. The mean age of the patients was 22.42 years and their mean BMI was 16.82. Patients with systolic dysfunction had lower hemoglobin and higher serum ferritin levels as compared to other patients. The study concluded that cardiac dysfunction is seen more in younger age, higher BMI, lower BP, low hemoglobin levels and raised serum ferritin levels. Thus, early intensive iron chelation therapy should be provided to all the patients to curb this dreaded complication.

Keywords: Iron overload, thalassemia, cardiomyopathy, iron chelation

Beta-thalassemia major is an inherited disorder of hemoglobin synthesis leading to ineffective erythropoiesis. There is absence of beta-globin chain synthesis but the production of alpha chains proceeds at a normal rate. These alpha chains accumulate to form toxic inclusion bodies and kill the developing erythroblasts in the marrow. The life of erythrocytes is shortened leading to severe hemolysis. The resultant profound hemolytic anemia stimulates erythropoietin release and compensatory erythroid hyperplasia in extramedullary tissues like liver and spleen. This erythroid hyperplasia leads to maxillary and frontal bone marrow expansion, thereby producing the characteristic 'chipmunk' facies appearance. Thalassemia patients require repeated blood transfusions to maintain their hemoglobin level. Repeated blood transfusions act as a necessary evil and create a state of iron overload in the body, affecting the heart, liver, pancreas, etc. Heart injuries in iron overload cause dilatation of atria and ventricles, arrhythmia, valvular dysfunction, pericarditis and finally heart failure in a few decades. Major risk factors causing cardiomyopathy are chronic anemia, reactive free oxygen radicals and iron overload. This devastating complication can be postponed by early intensive iron chelation therapy by deferoxamine, deferasirox and deferiprone.

However, despite therapeutic advancements, thalassemia cardiomyopathy still remains the leading cause of mortality in such patients. The aim of the present study was to determine the clinical and laboratory parameters associated with higher risk of cardiomyopathy.

METHODS

A cross-sectional study was done on 77 patients of beta-thalassemia major attending the Adult Thalassemia Day Care Centre at Lady Hardinge Medical College and Associated Hospitals in New Delhi during the period from January to March 2019. All the patients were confirmed for beta-thalassemia major by liquid

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chromatography. The patients underwent a detailed history and physical examination, with emphasis on cardiovascular features.

Further, their age, body mass index (BMI), blood pressure (BP), hemoglobin, serum ferritin level and two-dimensional echocardiography findings were analyzed for any statistical significance. All the patients were older than 18 years of age. Echocardiography was performed on the same machine and by a single person to eliminate intraobserver differences. Complete M-mode, two-dimensional, color flow mapping and Doppler studies were conducted on all the patients.

STATISTICAL ANALYSIS

Descriptive statistics was calculated for various parameters including demographic, hematological and echocardiographic features and are reported as, mean ± standard deviation (SD). Comparison of means of different parameters was done for normal versus systolic patients and normal versus diastolic patients to establish the significantly different parameters. $P < 0.05$ was considered statistically significant. All statistical analysis was done using GraphPad Prism software.

RESULTS

A total of 77 patients were screened, out of which 32 were female and remaining 45 were male. Sixty-three patients had diastolic dysfunction, 6 had systolic dysfunction and remaining 8 had normal left ventricular (LV) function. Out of the 6 patients with systolic dysfunction, 4 were male and remaining 2 were female.

The mean age of patients with systolic dysfunction was 18.33 years, while those with diastolic dysfunction were 21.97 years. The mean weight of all the patients was 46.4 kg, while those with systolic dysfunction were 41.5 kg.

The mean BMI was higher in patients with systolic dysfunction (19.03) as compared to those with diastolic dysfunction (16.6). The mean systolic and diastolic BPs of the patients was 106.98 and 71.58 mmHg, respectively. Both systolic and diastolic BPs were greater in patients with diastolic dysfunction as against patients with systolic dysfunction.

Almost all patients had hemoglobin of less than 10 gm%, with a mean of 9 gm%. Again, mean hemoglobin was more in patients with diastolic dysfunction (8.85) as compared to those with systolic dysfunction (8.5). Serum ferritin levels were raised with a mean of 2,914.67 ng/mL. The mean ferritin levels were 2,819.27 ng/mL in patients with diastolic dysfunction and 5,340.83 ng/mL in patients with systolic dysfunction. Echocardiography revealed the grade of diastolic dysfunction to be grade 1, 2 and 3 in 41, 17 and 5 patients, respectively. Pulmonary artery hypertension was found in patients with both systolic and diastolic dysfunction, with pressures higher in systolic dysfunction group (58.71 mmHg) as compared to diastolic dysfunction group (42.83 mmHg).

The mean left atrial volumes were more in patients with systolic dysfunction (76.07 mL) than in patients with diastolic dysfunction (69.52 mL). Mean E/A ratio was also more in systolic dysfunction group (1.11) as compared to diastolic dysfunction group (1.09). Further, mean E/E′ in patients with systolic dysfunction was 8.83 and those with diastolic dysfunction were 9.37. The comparison of mean values of demographic and hematological data of thalassemia patients and association with systolic and diastolic LV dysfunction has been depicted in Table 1 and Table 2, respectively. Comparison of mean values of echocardiography data of thalassemia patients and association with systolic and diastolic LV dysfunction has been depicted in Table 3 and Table 4, respectively.

Table 1. Comparison of Mean Values of Demographic and Hematological Data of Thalassemia Patients and Association with Systolic LV Dysfunction

Parameters	Normal LV function (n = 8)	Systolic LV dysfunction (n = 6)	P value at 95% significance level
Age (years)	29.13 ± 3.63	18.33 ± 0.44	0.000039
Male	2	4	-
Female	6	2	-
Height (cm)	1.76	1.47	0.000449
Weight (kg)	52	41.5	0.018458
BMI	16.724	19.03	0.013587
Systolic BP (mmHg)	117.5 ± 3.89	96.67 ± 3.65	<0.00001
Diastolic BP mmHg)	79.38 ± 4.13	63.33 ± 6.65	0.000448
Hemoglobin (gm%)	9.66	8.5 ± 0.5	0.004989
Serum ferritin (ng/mL)	2,914.67	5,340.83	0.049358

LV = Left ventricular; BMI = Body mass index; BP = Blood pressure.

Table 2. Comparison of Mean Values of Demographic and Hematological Data of Thalassemia Patients and Association with Diastolic LV Dysfunction

Parameters	Normal LV function (n = 8)	Diastolic LV dysfunction (n = 63)	P value at 95% significance level
Age (years)	29.13 ± 3.63	21.97 ± 3.78	<0.00001
Male	2	39	-
Female	6	24	-
Height (cm)	1.76	1.66	0.023417
Weight (kg)	52	46.298	0.01072
BMI	16.724	16.630	0.00325
Systolic BP (mmHg)	117.5 ± 3.89	106.63 ± 7.45	0.000179
Diastolic BP mmHg)	79.38 ± 4.13	71.38 ± 7.81	0.007044
Hemoglobin (gm%)	9.66	8.8	0.05107
Serum ferritin (ng/mL)	2,914.67	2,819.27	0.051291

Table 3. Comparison of Mean Values of Echocardiography Data of Thalassemia Patients and Association with Systolic LV Dysfunction

Parameters	Normal LV function (n = 8)	Systolic LV dysfunction (n = 6)	P value at 95% significance level
LVEF (%)	61 ± 1.7	36.67 ± 2.25	<0.00001
LA volume (mL)	48.39 ± 5.28	76.07 ± 7.66	<0.00001
E/A	1.39 ± 0.11	1.11 ± 0.31	0.0342
E/E'	6.26 ± 0.73	8.83 ± 0.91	<0.00001
IVRT (msec)	71.81 ± 3.88	79.92 ± 4.17	0.0028
LVDD (mm)	45.88 ± 4.53	79.79 ± 6.31	<0.00001
LVSD (mm)	28.57 ± 2.43	35.86 ± 4.55	0.0022
PASP (mmHg)	19.92 ± 2.56	58.71 ± 6.01	<0.00001

LVEF = Left ventricular ejection fraction; LA = Left atrial; E = Early diastolic transmitral flow velocity; A = Late (atrial) transmitral flow velocity; E' = Early diastolic mitral annular velocity; IVRT = Isovolumic relaxation time; LVDD = Left ventricular diastolic dysfunction; LVSD = Left ventricular systolic dysfunction; PASP = Pulmonary arterial systolic pressure.

Table 4. Comparison of Mean Values of Echocardiography Data of Thalassemia Patients Association with Diastolic LV Dysfunction

Parameters	Normal LV function (n = 8)	Diastolic LV dysfunction (n = 63)	P value at 95% significance level
LVEF (%)	61 ± 1.7	55.40 ± 2.83	<0.00001
LA volume (mL)	48.39 ± 5.28	69.52 ± 4.98	<0.00001
E/A	1.39 ± 0.11	1.09 ± 0.28	0.0039
E/E'	6.26 ± 0.73	9.37 ± 1.29	<0.00001
IVRT (msec)	71.81 ± 3.88	80.52 ± 3.86	<0.00001
LVDD (mm)	45.88 ± 4.53	69.82 ± 3.46	<0.00001
LVSD (mm)	28.57 ± 2.43	33.85 ± 3.03	<0.00001
PASP (mmHg)	19.92 ± 2.56	42.83 ± 4.96	<0.00001

DISCUSSION

Our study of 77 adult beta-thalassemia major patients has shown that cardiac dysfunction is seen more in younger age, higher BMI, lower BP, low hemoglobin levels and raised serum ferritin levels. Pulmonary artery pressure was more in patients with systolic dysfunction as compared to diastolic dysfunction.

One unit of packed red blood cells contains approximately 200-250 mg of iron.[1] After transfusion of approximately 20 units of red cells, ectopic iron deposition starts in tissues such as liver, pancreas, heart, etc. As iron overload progresses, transferrin is saturated and generation of free hydroxyl radicals is promoted, which causes iron deposition in tissues, leading to their cell death and fibrosis.[2] The heart is affected more than other tissues as it takes up labile iron in the plasma directly, which is toxic for the cardiac myocytes. Several guidelines support that early iron chelation therapy is beneficial in delaying cardiac dysfunction.[2]

Serum ferritin is a simple, noninvasive, easily available and reproducible test to assess iron overload in the body. It is also an acute phase reactant and so, it may be falsely elevated in infections and inflammation. Still, it remains the most widely used tool in evaluating iron overload. Moreover, ferritin levels <2,500 correlated with greater survival without heart disease and ferritin levels >2,500 correlated with increased death due to cardiomyopathy in patients of thalassemia.[3]

Two-dimensional echocardiography is another simple, noninvasive, reproducible test, which can be done

to detect cardiac dysfunction at an early stage and also, it can monitor the disease process. It has gained importance over the past few decades due to its ability to detect cardiomyopathy before clinical signs appear. Once the patient becomes symptomatic, the prognosis usually gets worse. Several studies in the past also indicate that echocardiography plays a significant role in early detection of cardiac dysfunction.[4]

Cardiac magnetic resonance imaging (MRI) can be done to measure iron deposition. However, it is expensive and not easily available, so cannot be used for serial monitoring. MRI T2 relaxation time of <20 msec indicates increased iron deposition and consequent lower ejection fraction.[5] However, there is no linear correlation between iron deposition and reduced ejection fraction.[6]

The currently available iron chelators include deferoxamine, deferasirox and deferiprone.[1] Deferoxamine is the oldest chelator, given parenterally and occasionally causes cataracts, deafness and local skin reactions like urticaria. It is given by slow infusion and the constant presence of the drug improves the efficacy of chelation and protects the tissues from occasional release of free iron radicals. Deferiprone is given orally, but causes agranulocytosis. Deferasirox is the latest iron chelator, which is given orally in a dose of 20-30 mg/kg, but may lead to renal impairment and gastric disturbances.

CONCLUSIONS

Thalassemia requires a special mention as it affects the life of the individual and the whole family. Cardiomyopathy occurs as a consequence of chronic anemia, damage by reactive free oxygen radicals and iron overload. Early detection, screening and monitoring of cardiac dysfunction should be done in each patient. Iron chelation therapy is of paramount importance and should be started at 5 to 8 years of age to delay the disease process. Bone marrow transplantation in beta-thalassemia has been found to be curative in 80% to 90% of patients, but the decision to transplant is best made in consultation with specialized centers as majority of patients survive into adult life.[7] Gene therapy in thalassemia is still inexperimental stages.

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