EVIDENCE OF ABNORMAL LEFT VENTRICULAR FUNCTION IN PATIENTS WITH THALASSAEMIA MAJOR: AN ECHOCARDIOGRAPHY BASED STUDY

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Background: Thalassaemia represent one of the most common single gene disorder causing a major public health problem in Pakistan. Nearly 100,000 people are born worldwide with this severe blood disorder every year. Over the last 3 decades, the development of regular transfusion therapy and iron chelation has dramatically improved the quality of life and transformed thalassaemia from a rapidly fatal disease to a chronic disease compatible with prolonged survival. Objective of this observational cross sectional study was to determine the effects of chronic anaemia and transfusional iron overload on the left ventricular function using Doppler echocardiography. **Methods:** This study was conducted in the Department of Paediatric Cardiology, The Children's Hospital & Institute of Child Health, Lahore, Pakistan from 1st April 2006 to 30th September 2007. The study comprised of 50 consecutive cases of beta-Thalassaemia major and 30 controls with normal haemoglobin and electrophoresis pattern. β-Thalassaemia major patients were diagnosed on the basis of haemoglobin electrophoresis. Patients with any congenital or acquired heart disease, concurrent infective disorder and with history of cardiac surgery were excluded from the study. 2-D, M-mode and Doppler echocardiography was performed in all the study cases and controls. Statistical comparison of study cases and controls was conducted by using unpaired *t*-test. **Results:** The age of the patients ranged from 2 years to 25 years with mean age of 9.65 years. Males were 34 (68%) and females were 16 (32%). None of the study cases was on regular chelation programme while 31 (62%) patients were on irregular chelation with single dose of intravenous desferrioxamine only at the time of blood transfusion. 19 (38%) of the patients had LV dysfunction in the form of isolated systolic dysfunction in 2 (4%), isolated diastolic dysfunction in 15 (30%) while global dysfunction in 2 (4%) of the patients. Left ventricular dimensions, stroke volume and E/A ratio were found considerably high in the study group. **Conclusion:** A very high percentage of Thalassaemia patients have cardiac involvement as LV dysfunction. This is mainly due to chronic anaemia, poor compliance with chelation therapy and non-availability of proper cardiac monitoring. Regular assessment of cardiac function may help a lot to improve the quality of life of these patients and may reduce the morbidity and mortality to a great extent.

Keywords: Beta Thalassaemia major, Echocardiography, Left ventricular dysfunction

INTRODUCTION

Thalassaemia represent one of the most common single gene disorder causing a major public health problem in Pakistan.[1] Near 100,000 people born world wide with this severe blood disorder every year.[2] Over the last three decades, the development of regular transfusion therapy and iron chelation has dramatically improved the quality of life and transformed Thalassaemia from a rapidly fatal disease to a chronic disease compatible with prolonged survival.[3] However, these conventional modalities are expensive, time consuming, and inconvenient. In developing countries, like Pakistan, poor availability of proper medical care, safe and adequate red blood cell transfusion together with high cost and poor compliance with chelation therapy remain major obstacles. Despite the increased life expectancy of Thalassaemia patients, complications keep arising. These relate to inadequate transfusions, transfusion transmitted viral diseases, iron overload related endocrine, liver and cardiac disturbances as well as toxicities of iron chelators.[4] Frequent blood transfusions necessary for treatment of Thalassaemia major, unfortunately carry the adverse side effect of iron build up in the body, which can damage the heart.[5] In fact cardiac disease is responsible for 70% of deaths in thalassaemia major patients.[6]

Congestive heart failure remains the primary cause of death in patients suffering from β-thalassaemia major.[7] Its early detection allows the prompt initiation of aggressive chelation therapy when condition can still be reversed.[8]

We studied 50 β-Thalassaemia major patients in order to determine the effects of chronic anaemia and transfusional iron overload on the left ventricular function using Doppler echocardiography because early detection of cardiac function impairment by echo-Doppler indices can assist in preventing further cardiac damage by modifying disease progression and treatment.

SUBJECTS AND METHODS

It was an observational cross sectional study from 1st April 2006 to 30th September 2007, conducted at the department of paediatric cardiology, The Children's

Hospital and the Institute of Child Health Lahore, Pakistan. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from each patient. Non probability purposive sampling technique was used. The study comprised of 50 cases of β-thalassaemia major and 30 controls with normal haemoglobin and electrophoresis pattern. Diagnosis of β-Thalassaemia major was made on the basis of haemoglobin 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 30 healthy children comparable in age and sex, free from any cardiovascular disorder and not taking any cardio active drugs. Detailed clinical examination and investigations including haemoglobin, chest X-Ray, electrocardiogram and serum ferretin levels were obtained in the study cases. Echocardiography (2-D, M-mode, Doppler) was performed in study cases and control group. General Electronics vivid-7 echocardiogram machine was used. Two dimensional, M-mode and Doppler echocardiographic assessment was performed using mechanical and phased array sector scanner with 4.5 MHz and 3.0 MHz transducers. The examination was conducted with the patient lying in supine position. The parasternal long axis and short axis and apical four chamber views were obtained in all study cases and control groups.

Echocardiographic Measurements:

The left ventricular end systolic and end diastolic dimensions, left ventricular posterior wall thickness and septal thickness, and fractional shortening (FS%) 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 isovloumetric relaxation time (IVRT) were calculated from each cardiac cycle. Systolic function was considered abnormal if the ejection fraction was less than 55% and the fractional shortening 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 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. Pseudonormal when E/A ratio was in normal range, but on valsalva manoeuvre, E/A dropped to less than normal or there was associated significant systolic dysfunction. Restrictive left ventricular function was labelled when E/A ratio was more than normal, deceleration time of E-wave and isovolumetric relaxation time were less than expected normal. Following cut-off values of mitral inflow velocities, deceleration time and isovolumetric relaxation time were used for diastolic dysfunction categorization according to different age groups.[9]

Factor \ Age Group	3–8 years	9–12 years	13–17 years	Adults
E–wave (cm/Sec)	92±14	86±15	88±14	67±14
A–wave (cm/Sec)	42±11	41±09	39±08	48±16
E/A	2.4±0.7	2.2±0.6	2.3±0.6	1.5±0.6
Deceleration time (mSec)	145±18	157±19	172±22	195±34
Isovolumetric relaxation time (mSec)	62±10	67±10	74±13	83±16

Data are expressed as Mean±SD. Statistical comparison of thalassemic patients and controls was conducted by using unpaired *t*-test. P-value of less than 0.05 was considered statistically significant.

RESULTS

In the study cases, age ranged from 2 years to 25 years with the mean age of 9.65 years. There were 34 (68%) males and 16 (32%) females in the study cases. None of the study cases was on regular five nights per week chelation therapy with subcutaneous or oral desferrioxamine. 31 (62%) of the cases were on irregular chelation with single dose of intravenous desferrioxamine only at the time of blood transfusion. Blood transfusion was started at a mean age of 1.6±1.1 years. Transfusion frequency was at a mean of 21.8±9.7 days. Signs of cardiac failure in the form of raised jugular venous pressure, gallop rhythm and basal crepts were noted in 2 (4%) patients. 6 (12%) patients had splenectomy. Mean pre-transfusion haemoglobin was 6.4±1.83 g/dl in the study cases. Serum ferretin level more than 5000 ηg/ml was present in 18 (36%) cases while the mean serum ferretin level for the whole study group was 4718±1925 ηg/ml. On chest X-ray, cardiomegaly was detected in 24 (48%) cases, while electrocardiograms of all the patients revealed regular sinus rhythm. Echocardiographic measurements (M-mode, 2-D, and Doppler) in patients with β-thalassaemia major and

controls are shown in Table-1. Abnormalities in LV function in the study group are summarised in Figure-1. Fifteen of the study patients had diastolic dysfunction. Grading of severity of diastolic dysfunction in these patients is shown in Figure-2.

Table-1: Echocardiographic measurements in patients with β-Thalassaemia major and control subjects (Mean±SD)

Echocardiography M-mode/2-D/Doppler	β-Thalassaemia Major Cases (n=50) Mean±SD	Controls (n=30) Mean±SD	*p*-value
IVSd (mm)	8.86±2.19	7.05±1.72	<0.05
LVIDd (mm)	36.8±3.52	31.4±3.67	<0.05
LVIDs (mm)	23.6±3.67	19.2±2.75	<0.05
LVPWd (mm)	8.74±2.37	6.45±1.62	<0.05
FS %	36.4±3.92	32.2±2.68	<0.05
EF %	68.5±7.23	64.3±6.45	<0.05
SV	35.8±8.73	25.4±7.33	<0.05
E-wave (cm/Sec)	101.2±19.5	84.3±21.2	<0.05
A-wave (cm/Sec)	41.4±9.5	33.7±10.3	<0.05
E/A	2.42±0.52	1.91±0.61	<0.05
DT (mSec)	155±26	149±24	>0.05
IVRT (mSec)	62±13	59±14	>0.05

(IVSd: Interventricular septum in diastole, LVIDd: Left ventricular internal dimension in diastole, LVIDs: Left ventricular internal dimension in systole, LVPWd: Left ventricular posterior wall in diastole, FS: Fractional shortening, EF: Ejection fraction, SV: Stroke volume, DT: Deceleration time, IVRT: Isovolumetric relaxation time)

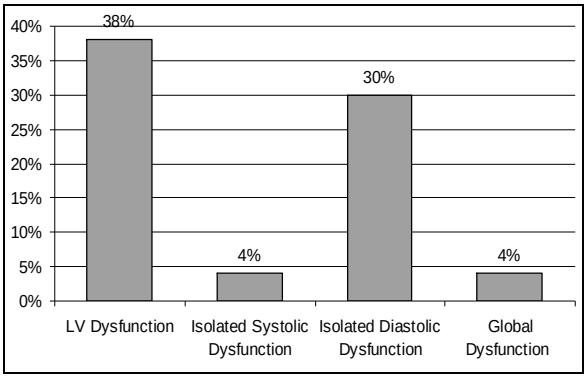

Figure-1: Abnormalities in LV Function (n=50)

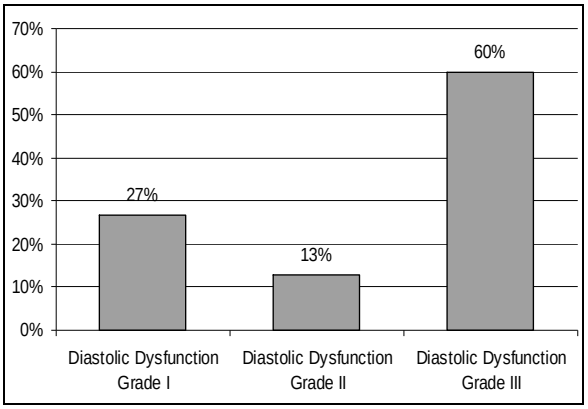

Figure-2: Grading of Severity of Diastolic Dysfunction (n=15)

DISCUSSION

β-thalassaemia is an inherited haemoglobin disorder resulting in chronic anaemia. Thalassaemia major is characterized by the onset of the disease during the first year of life and requiring life long blood transfusion therapy for survival. In these patients, this long term transfusion therapy, extravasal haemolysis, an increased intestinal absorption of iron result in systemic iron overload. This iron is deposited in many organs of body like liver, pancreas, thyroid glands and heart causing permanent damage to them. Iron-induced cardiac disease is considered to be the primary cause of death in patients who have transfusion dependent β-thalassaemia major.[10] Myocardial iron deposition causes cardiac hypertrophy, dilatation and degeneration of myocardial fibres.[11] Iron deposition is mainly within the ventricles and can be patchy.[4] The unbound iron generates toxic oxygen metabolites resulting in further injury to myocytes. Therefore thalassaemic patient develop conductive disturbances and progressive heart failure. Although, heart complications are the leading cause of death and one of the main causes of morbidity, but regular assessment of cardiac status recognises the early stages of heart disease and allows for prompt intervention.[12] 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. This is a simple, non invasive way of recording early cardiac alterations in thalassaemia major patients and enables long-term monitoring of cardiac function in the assessment of the effectiveness of the chelation therapy.[13] In this study, we found that inter-ventricular 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-thalassaemia patients had cardiac enlargement with high stroke volume. Bosi G *et al*, Chotivittayatarakorn *et al*, Kremastinos DT *et al* and Aessopos *et al* reported that the left ventricular diameter in the thalassaemic patients were significantly higher than in controls, which is in concordance with present study.[5,14–16]. The failure to detect impaired ventricular systolic function is not surprising since the haemodynamic effects associated with anemia helped to maintain normal ejection fraction and myocardial fibre shortening. Atiq M *et al* reported that 23% of their study patients had LV systolic while 29% had diastolic dysfunction.[17] LV systolic dysfunction in 23% of patients is a higher percentage than our finding but their study comprised of those

thalassaemia patients who clinically had some symptoms and were actually referred for cardiac evaluation. Aldouri MA *et al* demonstred that the interventricular septal thickness and left ventricular posterior wall thickness of the thalassaemic 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 P *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.[14,18] While 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.[19] 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 9 (18%) 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 thalassaemia major and controls for Doppler diastolic indexes obtained from analysis of transmitral flow, which is not consistent with our finding.[20] 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.[21] In contrast, we found 30% 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.[22]

CONCLUSION

To conclude, we found the concordant results with previous studies as far as the LV dimensions and systolic dysfunction is concerned but we found a quite higher percentage of diastolic dysfunction in our study which is most likely due to poor compliance with chelation therapy and non availability of proper cardiac monitoring. It is known that the median period of time between an abnormal LV ejection fraction reading and development of cardiac failure is three and a half years—enough time for treatment with desferrioxamine to prevent and reverse the severe heart dysfunction. Monitoring cardiac function can be a useful index as to the over all prospects for an individual patient. The demonstration of impaired myocardial function might not only serve to alert the clinicians to give 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 programme is required to prevent an inexorable progression to severe cardiac failure. Early detection of cardiac dysfunction may help a lot to improve the quality of life of these patients and may reduce the morbidity and mortality to a great extent. Assessment of cardiac function by echocardiography on regular basis is a useful tool for this purpose.

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