Original Research Paper Pediatrics

CARDIAC ABNORMALITIES IN TRANSFUSION DEPENDENT BETA THALASSEMIA CHILDREN

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ABSTRACT

Objectives: To note spectrum of cardiac abnormalities in transfusion dependent β-thalassemia children by clinical and echocardiographic evaluation and to correlate its severity with serum ferritin levels.

Methods: 100 thalassemic children who received >50 blood transfusions and had serum ferritin level >2500 ng/ml were included. Detailed medical history, anthropometry, transfusion details, examination including cardiovascular system were noted. Echocardiogram, Colour Doppler and Tissue Doppler Imaging (TDI) were done to assess cardiac functions. Cardiac dimensions, functions, mass and index were assessed by standard Echocardiographic techniques and were compared to paediatric norms. TDI was performed to assess myocardial involvement.

Results: Cardiac symptoms were largely subclinical. 13 children had tachycardia and 10 were hypertensive. 8/100 had left ventricular dilatation. 85 children had diastolic dysfunction which was seen more in children with Hb <8 g/dL, increasing years of transfusion therapy and increasing ferritin levels (p value: 0.042). 13/100 children had systolic dysfunction. There was a significant correlation between age and systolic dysfunction (p value: 0.017). 32 children had a high cardiac output. There was a significant correlation between increasing serum ferritin levels and TDI abnormalities (p value: 0.006). 45 children had right ventricular dysfunction. There was significant correlation between age and right ventricle dysfunction (p value: 0.028).

Conclusion: Cardiovascular manifestations remain predominantly silent in thalassemic children. On Echocardiographic evaluation, LV dilatation, LV diastolic and systolic dysfunctions, impaired myocardial performance, increased cardiac output, moderate TR and RV dysfunction were the various findings. LV diastolic dysfunction was more common than systolic dysfunction and was noted more in children with longer duration of transfusion therapy and high serum ferritin levels. TDI complimented the conventional echocardiography in diagnosing diastolic dysfunction.

KEYWORDS : Thalassemia, Tissue Doppler imaging, Echocardiography, Iron Cardiomyopathy

Introduction:

β-thalassemia is the commonest inherited haemoglobin disorder resulting in chronic hemolytic anemia.[1] Over thirty thousand children are born in India every year with this disorder.[2] Besides regular blood transfusions, management of these children include chelation therapy for diminishing the unintended effects of transfusion induced iron overload on critical organs such as the heart, liver, pancreas and gonads; with iron cardiomyopathy being one of the most serious conditions causing mortality in these patients. Congestive heart failure and fatal cardiac tachyarrhythmias leading to sudden cardiac death are seen within three months to one year after onset of cardiac symptoms. In clinical practice, serum ferritin is used to assess the effectiveness of chelation therapy and degree of iron overload. However, most of the cardiac symptoms remain largely subclinical. Initial cardiac changes have been documented by conventional echocardiography before clinical; electrocardiogram (ECG) or radiological manifestations became apparent.[3] Though literature reveals that severity of cardiac overload can be detected by cardiac magnetic resonance imaging (MRI), it is rather impractical and economically not feasible to perform serial MRI studies in the long term management of these transfusion dependent children in developing countries such as India. This prompted us to conduct a study to assess cardiac manifestations of iron overload in thalassemic children by the conventional, non-invasive modality of 2D- Echocardiography with Color Doppler and Tissue Doppler Imaging (TDI).

Materials and methods:

An observational study was conducted in B. J. Wadia Hospital for Children, Mumbai. 100 thalassemic children above two years of age who had received at least 50 blood transfusions and/or had a serum ferritin level >2500 ng/ml were included. Children with congenital heart disease (CHD) or acquired heart disease were excluded. A comprehensive medical history including transfusion details was noted. Previous maintained records of the child's growth, compliance to medications and complications of the disease were obtained when required. General, anthropological and systemic examination including detailed cardiovascular system examination was carried out. Results of 2D Echocardiogram, Colour Doppler and TDI were recorded.

Cardiac functions, mass and index were assessed by standard Echocardiography techniques. Left ventricular (LV) systolic function was calculated by measuring the left ventricular end diastolic dimension (LVIDd), left ventricular end systolic dimension (LVIDs)[4,5,6] and evaluating the ejection fraction (EF; normal value: 56-78%) and fractional shortening (FS; normal value: 28-44%).[7] LV diastolic function was studied by evaluating the Doppler imaging by noting the mitral inflow (MV) tracing i.e. MV 'E' velocity and MV 'A' velocity, MV E/A ratio and pulmonary venous (PV) tracings such as PV 'S' (systolic) velocity, PV 'D' (diastolic) velocity and S/D ratio.[8,9,10] Left-ventricular mass (LVM) was calculated using the Devereux formula[11] and LVM index (LVMI) was calculated by dividing LVM by body surface area (BSA) to minimize effects of age, gender and body weight status.

Right Ventricle (RV) function was assessed by Tricuspid Annular Plane Systolic Excursion (TAPSE)[12,13], RV area in diastole and RV Fractional Area Changes (FAC). Cardiac output (CO) index was calculated by dividing the CO by body surface area (BSA) (normal value: 3.5–5.5 l/min/m^2) regardless of patient age and size.(Tibby *et al.* 2003) [13]

Tissue Doppler Imaging was performed to assess myocardial systolic functions (Sa wave), early myocardial diastolic function (E' wave), late myocardial diastolic function (A' wave), E'/A' ratio, E/E' ratio. TDI reports were defined as abnormal if the Sa wave value <63 cm/sec, E' wave <13 cm/sec, A' wave <3.8 cm/sec, E'/A' ratio <2 and E/E' ratio >10.[14]

Treatment strategies:

The children received regular transfusion therapy as per protocol guidelines. Management of iron overload involved administration of appropriate dosage of iron chelators and monitoring the compliance to treatment.

Statistical Analysis:

Descriptive statistics of continuous variables were expressed as mean and standard deviation. Discrete variables were presented as frequencies and group percentage. All continuous variables were tested for normal distribution by D'Agostino-Pearson normality test. Student's t-test was used to compare the means of continuous normally distributed data. Categorical data were tested using the chi-square test. All statistical tests were 2-tailed, and a p value of 0.05 was considered statistically significant. Data was analyzed using SPSS 17.0 software for Windows.

Results:

Out of 100 children in the study, 91 children suffered from thalassemia major and nine from thalassemia intermedia. 16 subjects had undergone splenectomy for hypersplenism. 78 children were on iron chelation therapy in the form of either deferasirox (59 children) or deferiprone (19 children) while 22 children were not on any iron chelating drugs despite their serum ferritin being high. Cardiac findings were largely subclinical with only 13 children having tachycardia and 10 being hypertensive for their age. Mean hemoglobin level (Hb) was 8.5 g/dl (range: 6.0-10.6 g/dl) and mean ferritin level was 5252 ng/ml (range: 2724-10900 ng/ml). Out of the 16 splenectomised children, Ten had Hb level <8 g/dl while the remaining six had Hb level between 8-10 g/dL. Splenectomy had been performed in 12.9% children having serum ferritin 2500-5000 ng/ml, 11.7% of children having serum ferritin 5000-7500 ng/ml and 50% of children having serum ferritin 7500-10000. Percentage of splenectomy was more in age group having serum ferritin level of 7500-10000.

A. Assessment of cardiac functions by Echocardiographic parameters:

I. Left ventricular systolic functions: Eight of the 100 children had left ventricular dilatation. 13 children had systolic dysfunction of which four were 4-7 yrs of age, three were 8-11 yrs of age and six were 12-15 yrs of age as illustrated in **figure 1**. There was a significant correlation between age and systolic dysfunction (p value: 0.017).

figure 1

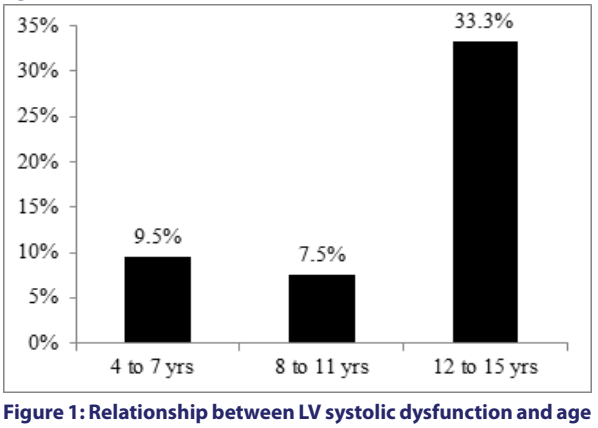

Figure 1: Relationship between LV systolic dysfunction and age of subjects

Left ventricular systolic abnormalities were seen in 9.3% of children having serum ferritin level between 2500-5000 ng/ml, 14.7% of children having serum ferritin between 5000-7500 ng/ml, 20% of children having serum ferritin level of 7500-10000 ng/ml and 50% of children having serum ferritin more than 10000 ng/ml.

ii. Left ventricular diastolic dysfunction: 85/100 thalassemic children showed diastolic dysfunction. It was observed that the proportion of children having diastolic dysfunction increased as number of years with transfusion therapy increased as illustrated in **figure 2**. Under the age of five years, 79.2% children, between the age of 5-9 years 86.3% children and between the age of 10-15 years 88% children show early diastolic dysfunction.

45, 40 and 15 out of the total 100 children had Hb levels of 8 g/dl, 8-10 g/dl and >10 g/dl respectively. Of these 41/45 (91.1%), 34/40 (85%) and 10/15 (66.6%) children showed the presence of diastolic dysfunction on echocardiography. Thus anemia could be one of the important factors leading to diastolic dysfunction. Further diastolic dysfunction was present in 42/54 (77.8%) children having serum ferritin level between 2500-5000 ng/ml, 33/34 (97.1%) children having serum ferritin level 5000-7500 ng/ml, 9/10 (90%) having serum ferritin level 5000-7500 ng/ml and 1/2 (50%) in children having serum ferritin level >10000 ng/ml. There was a significant correlation found between serum ferritin and diastolic dysfunction (p value: 0.042). It was observed that diastolic dysfunction was more pronounced than systolic dysfunction in children with thalassemia.

Figure 2

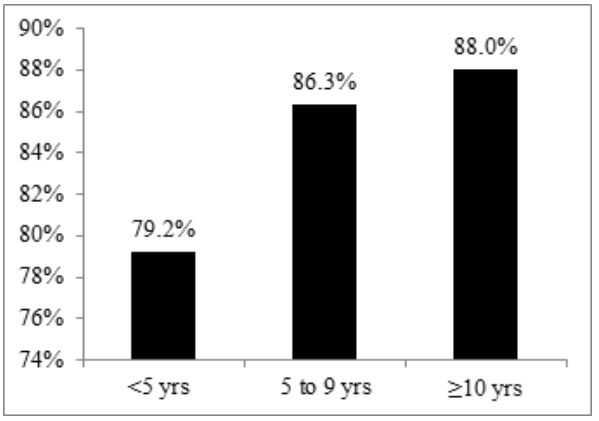

Figure 2: Relationship between diastolic dysfunction and duration of transfusions

iii. Left ventricle cardiac index: In present study 32 out of 100 patients had high cardiac output. There was significant correlation between age and left ventricular cardiac index (p value: 0.027).

B. Assessment of cardiac functions by Tissue Doppler Imaging (TDI):

Various forms of TDI abnormalities were detected in 97% thalassemic children. 2% subjects had abnormal E' and 89% had abnormal E/E'. Of these 89 children, 40 belonged to age group of 4-7 years, 36 belonged to age group of 7-11 years and 13 belonged to age group of 12-15 years. There was significant correlation present between age and E/E' (p value: 0.032) as illustrated in **figure 3**. TDI abnormalities were found in 53/54 children having serum ferritin level between 2500-5000 ng/ml, 33/34 children having serum ferritin level between 5000-7500 ng/ml, 10/10 children having serum ferritin level 7500-10000 ng/ml and 1/2 children having serum ferritin level more than 10000 ng/ml. There was significant correlation found between serum ferritin level and TDI abnormalities (p value: 0.006).

Figure 3

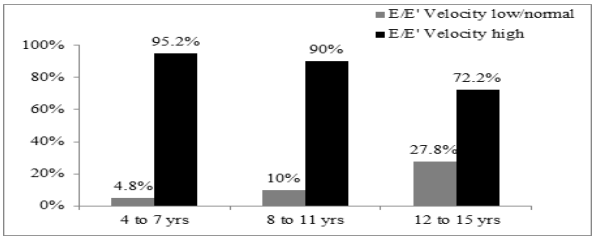

Figure 3: Relationship between age of subjects and TDI parameter E/E'

C. Assessment of Right ventricular functions:

It was found that 36% had abnormal FAC and 9% had abnormal TAPSE. Tricuspid regurgitation (TR) was detected in 25 children of which 24 were of mild grade and one was of moderate grade. 47 out of 100 had high RV cardiac index. In all, 45/100 had abnormal right ventricular function. There was significant correlation between age and right ventricle dysfunction (p value: 0.028). When right ventricular functions were compared to mean Hb it was found that, 11/15 (73.3%) children having Hb>10g/dl, 18/40 (45%) children having Hb between 8-10 g/dl and 16/45 (35.6%) of children having Hb value <8 g/dl had right ventricle dysfunction. On comparing the right ventricular functions to serum ferritin it was found that 27/54 (50%) having serum ferritin level between 2500-5000 ng/ml, 14/34 (41.2%) having serum ferritin level between 5000-7500 ng/ml, 3/10 (30%) having serum ferritin level between 7500-10000 ng/ml and 1/2 (50%) having serum ferritin level more than 10000 ng/ml had right ventricular dysfunction.

Discussion

β-Thalassemia is an inherited hemoglobin disorder resulting in chronic hemolytic anemia that typically requires life-long transfusion therapy. Although traditionally prevalent in the Mediterranean basin, its rising prevalence in Middle East, India and Southeast Asia has rendered β-thalassemia a global health problem. Cardiac complications represent the primary cause of mortality and one of the major causes of morbidity in these patients. Heart disease is mainly expressed by cardiomyopathy that progressively leads to heart failure and death. The β-thalassemia cardiomyopathy is mainly characterized by two distinct phenotypes, a dilated phenotype, with left ventricular dilatation and impaired contractility and a restrictive phenotype, with restrictive left ventricular filling, pulmonary hypertension, and right heart failure. The pathophysiology of the disorder is multifactorial, with a central role of myocardial iron overload and the significant contribution of immune-inflammatory mechanisms. Echocardiography remains an indispensable tool in the cardiovascular assessment of patients, it provides many insights into cardiovascular functions and its use allows improved management of these patients.

During the study, 100 thalassemic children were studied to detect cardiovascular structural and functional abnormalities and its correlation with serum ferritin. There was significant correlation between age and systolic dysfunction. Abnormalities in systolic function were more in age group between12-15 yrs. It was noted that as serum ferritin level increased, percentage of LV systolic functions abnormalities increased. These findings were similar to the study conducted by Papadopoulou-Legbeloul et al[15] on 93 patients, aged 2.5 to 18 years old (mean age 11.9 ± 4.6 years) affected by β-thalassemia major. 6/93 patients (6.5%) had increased LVDd. The mean value of EF and FS was lower compared to the control group and had a statistically significant difference (p value: 0.01).

It was observed that percentage of diastolic dysfunction increased as the years of transfusion therapy increased. A significant correlation was found between serum ferritin and diastolic dysfunction. Also the diastolic dysfunction was more pronounced than systolic dysfunction. Cardiac index (CI) is a vasodynamic parameter that relates the cardiac output (CO) to body surface area (BSA), thus relating heart performance to the size of the individual. Anemia related increased CO, resulting in increased workload on the heart contributes to the development of cardiac dysfunction in thalassemic children. Anemia together with marrow expansion leads to volume overload that then demands increased contractility.

Tissue Doppler Imaging (TDI) is a fairly new and an easy method to detect abnormal myocardial iron overloading in pediatric and adult patients with β-thalassemia. It has 88% sensitivity and 65% specificity compared to the gold standard MRI T2*. TDI measures early myocardial diastolic function i.e. E' and late myocardial diastolic dysfunction i.e. E/E'. On TDI it was observed that diastolic dysfunction was more pronounced than systolic dysfunction. Iron deposition in the heart may be patchy, non uniform and is known to accumulate in the septum as well as the free wall of the ventricles. The regional abnormalities are related to iron overload and are easily detectable with TDI. Wall motion abnormalities may represent an early sign of cardiac disease despite preserved global function. 45% had abnormal right ventricular function. There was significant correlation between age and right ventricle dysfunction.

Long-term, prospective studies in larger numbers of pediatric patients with β-thalassemia would be needed for echocardiographic assessment of systolic and diastolic left ventricular functions, right ventricular functions and Tissue Doppler Imaging. TDI should be a routine part of the echocardiographic assessment of all pediatric patients of β-thalassemia.

Conclusion:

Cardiovascular manifestations remain predominantly silent in thalassemic children. On conventional Echocardiographic evaluation, LV dilatation, LV diastolic dysfunction, LV systolic dysfunction, impaired myocardial performance, increased Cardiac output, moderate TR, RV dysfunction were the various abnormalities found. LV diastolic dysfunction was more commonly noted than systolic dysfunction. The diastolic dysfunction was more pronounced in children with an increased duration of transfusion therapy and an increasing serum ferritin levels. Tissue Doppler Imaging complimented the conventional echocardiography in picking up diastolic dysfunction early and can be easily evaluated on the present day Echocardiography machines.

Acknowledgement: Authors wish to thank the Medical Director, Dr Y.K Amdekar, B.J. Wadia Hospital for Children for allowing us to do the study and publish this research paper.

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