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Research Article

Cardiac abnormalities in patients with beta thalassemia

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ABSTRACT

Background: Thalaseemias are a group of chronic, inherited anemias characterized by defective hemoglobin synthesis and ineffective erythropoiesis. The presence of chronic anemia and transfusional iron overload exacerbates congestive cardiac failure. Cardiac disease remains the major cause of death in thalassemia major. The objective was to assess cardiac status in patients with transfusion dependent thalassemia.
Methods: A prospective observational study was conducted at thalassemia Centre in tertiary care institute. 32 patients with transfusion dependent beta thalassemia were enrolled. A detailed history, clinical examination and cardiac investigations were conducted in enrolled patients.
Results: Symptoms and signs of cardiac disease were present in 5 (15.6%) patients. Cardiomegaly was observed on chest radiography in 23 (71.87%) patients. Only 3 (9.37%) patients had electrocardiographic abnormalities. Left Ventricular Ejection Fraction (LVEF) on 2-D echocardiography was ≥60% in all the 32 patients. Diastolic dysfunction and restrictive physiology on Doppler echocardiography was present in 19 (59.37%) patients and absent in remaining 13 (40.63%) patients.
Conclusions: Diastolic dysfunction is an early sign of myocardial dysfunction in patients with beta thalassemia.

Keywords: Diastolic dysfunction, Cardiomegaly, Thalassemia

INTRODUCTION

Thalassemia is among the most common genetic disorders worldwide. It is estimated that world over there are >200 million carriers of β-thalassemia gene, 40 million of them are in India alone. Every year approximately 1 lakh children with thalassemia major are born world over, of which 10,000 are born in India. The carrier rate for β-thalassemia gene varies from 1-2% in southern India to 3-15% in northern India.[1] Cardiac disease remains the major cause of death in thalassemia major. In beta thalassemia major, transfusions and iron chelation therapy have significantly improved the survival and reduced the morbidity.[2] In the 1960's 80% of patients had died by the age of 16 and now at least 80% survive beyond the age of 40 yrs. This improvement is unique, as no other formerly fatal genetic defect has shown such a benefit. However, heart complications still represent significant morbidity and remain the leading cause of mortality in transfusion dependent thalassemia (TM) patients.

Objective

The objective of this study was to assess cardiac status in patients with transfusion dependent thalassemia.

METHODS

The present prospective observational study was conducted at Thalassemia Centre in LTMMC and GH, Sion, Mumbai, India over a period of 2 years. A total of 32 transfusion dependent thalassemic patients who were registered at the outdoor thalassemia transfusion center at the same institute were enrolled in the present study. Informed consent was taken from patients or their parents and Institutional Ethical Committee approval was obtained. Thalassemic children >7 years of age who were on regular blood transfusions, irrespective of chelation were included in the study.

A detailed history and examination findings were noted in a predesigned proforma. The symptoms suggestive of cardiac disturbance were elicited by the following history- history of dyspnoea, chest discomfort, pedal edema, syncope, palpitations, history of cardiac failure in the past and history of medications for cardiac dysfunction (ACE inhibitors, diuretics, anti-arrhythmics, digoxin).

A detailed physical examination was done in each case and the vital parameters, signs of congestive cardiac failure and size of liver and spleen were noted. Chest X-ray, electrocardiogram (ECG) and 2-dimensional and Doppler echocardiography were done.

A posteroanterior chest X-ray was taken during mid-inspiration with the patient in an upright position for the measurement of cardiac size. The CT ratio was obtained by relating the largest transverse diameter of the heart to the widest internal diameter of the chest. A CT ratio of more than 0.5 indicated cardiomegaly.

Ventricular hypertrophy and cardiac rhythm disturbances were seen on ECG. Criteria used for ventricular hypertrophy was taken as given in 'The Harriet Lane Handbook, 17th edition' which are as follows

a. Right ventricular hypertrophy (RVH) criteria must have at least one of the following.

Increased right and anterior QRS voltage (with normal QRS duration):

- R in lead V1 >98th percentile for age.
- S in lead V6 >98th percentile for age.
- Upright T wave in lead V1 after 3 days of age to adolescence.

***Supplemental criteria*:**

- Presence of q wave in V1 (qR or qRs pattern).
- Right axis deviation (RAD) for patient's age.
- Right ventricle (RV) strain (associated with inverted T wave in V1 with tall R wave).

Left ventricular hypertrophy (LVH) criteria

Increased QRS voltage in left leads (with normal QRS duration):

- R in lead V6 (and I, aVL, V5) >98th percentile for age.
- S in lead V1 >98th percentile for age.

Supplemental criteria

- Left axis deviation (LAD) for patient's age,
- Volume overload (associated with Q wave >5 mm and tall T waves in V5 or V6),
- Left ventricle (LV) strain (associated with inverted T wave in leads V6, I, or aVF).

2D echocardiography and colour Doppler was done in all patients. Echocardiography and colour Doppler was done 7 days after transfusion only if hemoglobin was >10 gm%

The data obtained was analysed using the SPSS 15 software by applying Chi-square test. A 'p' value <0.05 was considered statistically significant.

RESULTS

A total of 32 multiply transfused thalassemic patients were enrolled for the study. The youngest patient was 9 years old and the oldest was 24 years old. A total of 21 (65.6%) males and 11 (34.4%) females were studied as shown in Table 1.

Table 1: Age and gender wise distribution of patients (n=32).

Age groups (years)	Gender		Total (%)
	Male (%)	Female (%)	
7-10	2 (6.25%)	2 (6.25%)	4(12.50%)
10-15	10 (31.25%)	4 (12.50%)	14(43.75%)
More than 15	9 (28.12%)	5 (15.62%)	14(43.75%)
Total	21 (65.60%)	11(34.40%)	32(100%)

Table 2: Age wise distribution of diastolic dysfunction on Doppler echo (n=32).

Age groups (years)	Presence of diastolic dysfunction (%)	Absence of diastolic dysfunction (%)	Total (%)
7-10	2(6.25%)	2(6.25%)	4(12.50%)
10-15	8(25.0%)	6(18.7%)	14(43.75%)
More than 15	9(28.1%)	5(15.6%)	14(43.75%)
Total	19(59.4%)	13(40.6%)	32(100%)

Mean pretransfusion hemoglobin of the enrolled patients was 8.5gm%. Out of 32 patients, 28 were taking deferiprone, 3 were on desferrioxamine and 1 patient was taking combination chelation therapy. Five (15.6%) patients had symptoms related to cardiac disease and all of them were more than 13 years of age. On examination, following signs of cardiac disease were noted- pedal edema, raised JVP, hepatojugular reflex, Gallop rhythm, basal rales and rhythm disturbances. All the 5 (15.6%) patients having signs of cardiac abnormality (CCF, arrhythmias) were more than 19 years of age. Cardiomegaly on chest radiograph was present in 23 (71.88%) patients. Only 3 (9.4%) patients had electrocardiographic (ECG) abnormalities.

Table 3: Correlation of diastolic dysfunction on Doppler echo with cardiomegaly on radiograph (n=32).

Cardiac abnormalities	Presence of diastolic dysfunction (%)	Absence of diastolic dysfunction (%)	Total (%)
Presence of Cardiomegaly on radiograph	17 (53.1%)	6 (18.8%)	23 (71.9%)
Absence of Cardiomegaly on radiograph	2 (6.2%)	7 (21.9%)	9 (28.1%)
Total	19 (59.4%)	13 (40.6%)	32 (100%)

p value 0.007.

Table 4: Correlation of diastolic dysfunction on Doppler echo with mean pre-transfusion hemoglobin (n=32).

Mean pre-transfusion hemoglobin	Presence of diastolic dysfunction (%)	Absence of diastolic dysfunction (%)	Total (%)
< 9 gm%	13 (40.6%)	9 (28.1%)	22 (68.8%)
≥ 9 gm%	6 (18.8%)	4 (12.5%)	10 (31.2%)
Total	19 (59.4%)	13 (40.6%)	32 (100%)

p value 0.96

All 3 patients having ECG abnormalities had signs of congestive cardiac failure on clinical examination and cardiomegaly on chest radiograph. All the 32 patients had normal left ventricular ejection fraction i.e. LVEF (LVEF ≥60%).

Table 2 shows that diastolic dysfunction/ restrictive physiology on Doppler echocardiography was present in 19 (59.4%) and absent in 13 (40.6%) patients. Diastolic dysfunction was present in all 5 patients having signs of congestive cardiac failure as well as all 3 patients with ECG abnormalities. Out of 19 patients having diastolic dysfunction, cardiomegaly on chest radiograph was present in 17 patients. (p value 0.007) as shown in Table 3. No significant association was found between diastolic dysfunction and mean pretransfusion hemoglobin (p value 0.96) as depicted in Table 4.

DISCUSSION

Heart complications represent significant morbidity and remain the leading cause of mortality in transfusion dependent thalassemia patients. Cardiac structure and function in thalassemia are mainly affected by two competing factors: iron overload and increased cardiac output (CO). The cardiac iron deposition results in a decrease of left ventricular function. The anaemia together with marrow expansion leads to volume overload and increased CO that then demands increased contractility adding additional stress to the heart (Starling's Law). Cardiac dysfunction in thalassemia manifests with congestive cardiac failure (CCF), arrhythmias and ultimately, premature deaths. In some cases, this was because of the difficulty in accepting the chelation treatment, which was cumbersome, but also occurred even in some patients who accepted the chelation therapy well.[3,4] Despite the advances in therapeutic management of thalassemia major and the resulting substantial improvement of patients' survival, heart disease always represented and still remains the primary cause of mortality and a major cause of morbidity.[5-8]

The average age of onset of cardiac failure in thalassemia patients was 16 years before initiation of regular transfusion therapy and chelation.[5] However regular transfusion and chelation therapy has increased the age of onset of cardiac failure in thalassemia. In a study of heart failure in 52 patients with beta thalassemia done by Kremastinos DT et al, mean age of onset of heart disease was 24 years.[9] 37% of patients with β-thalassemia major had cardiac disease at a mean age of 23 years was shown by Olivieri et al.[10] The mean age of the patients having signs of congestive cardiac failure in our study was 21.4 years.

Mancuso L et al studied Electrocardiographic abnormalities in thalassemia patients with heart failure and concluded that new onset ECG abnormalities are always evident in patients with and always absent in patients without heart failure due to thalassemic cardiomyopathy.[11] All patients with ECG abnormalities in our study had signs of cardiac failure. ECG may reveal heart failure due to iron overload late in the course of the disease, but it is not very sensitive for early detection of cardiac dysfunction.

All the 32 patients had normal left ventricular ejection fraction. (LVEF ≥60%) as assessed by 2-D Echocardiography. Among the 32 patients studied,

diastolic dysfunction on Doppler echocardiography was present in 19 (59.37%) patients and absent in remaining 13 (40.63%) patients. Out of 19 patients having diastolic dysfunction, cardiomegaly on chest radiograph was present in 17 patients. (p value 0.02) Observations similar to our study were made by Hou et al, Hankins et al and Spirito et al.[12-14] Spirito et al studied 32 patients with thalassemia major and found impaired diastolic Doppler indices in patients having normal systolic function.[14] Hankins et al studied 47 patients with transfusion dependant anemias.[13] While most patients had normal LV systolic function, 42% patients had signs of diastolic dysfunction, suggesting diastolic dysfunction to be an early sign of myocardial dysfunction in cardiac hemosiderosis. Hou et al in their study of 45 thalassemic children similarly showed that Left ventricular diastolic filling variables by echocardiography are important predictors of the outcome of patients with transfusion-dependent beta-thalassemia major.[12]

Similar conclusion was mad by Kremastinos et al and Iarussi et al.[15,16] Kremastinos et al in a study of 88 thalassemic children and Iarussi et al in a study of 30 thalassemic children concluded that Doppler diastolic indexes in beta-thalassemia major patients with normal left ventricular systolic function are similar to those seen in conditions with an increased preload, probably because of chronic anemia.[15,16] In yet another study by Leonardi, it was found that in patients with transfusion dependent thalassemia, echocardiographic diastolic function parameters correlated poorly with Ejection Fraction.[17]

Transfusion dependent thalassemia patients with normal systolic function have been shown to have impaired diastolic Doppler indices with restrictive filling pattern.[18] These latter signs were questioned as to their predictive value and have been attributed solely to increased CO.[15] Consistently, in a recent study, standard Doppler left ventricular filling pattern and pulsed Doppler tissue imaging parameters in thalassemia were similar to those seen in conditions of increased preload.[19] In contrast, in a 5 year follow-up study which assessed left ventricular diastolic filling variables by echocardiography, it was found that these were important predictors of the cardiac outcome in thalassemia patients.[16] Similarly in a recent study that followed thalassemia patients over a 10 year period, under regular constant transfusion-chelation treatment, some of the diastolic and systolic indices were able to predict the potential for cardiac risk.[18]

Doppler Echo and tissue Doppler studies can only identify the damage rather than delineating the cause, so limitation exists in predicting iron overload by Doppler Echo measurements.[20]

CONCLUSION

Diastolic dysfunction on Doppler echocardiography is an early sign of myocardial dysfunction in patients with beta thalassemia. ECG abnormalities detect heart failure due to iron overload late in the course of the disease, and therefore ECG is not very sensitive for early detection of cardiac dysfunction.

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