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Original Research Article

A study of echocardiographic changes in patients of thalassemia major

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ABSTRACT

Background: Thalassemia major is a chronic hematological disorder. Regular blood transfusion is the only modality of long-term survival for these patients. This leads to iron overload, the heart being the most severely affected organ. The gold standard for detecting myocardial iron deposition is cardiac MRI. However, very few patients can afford this investigation. Hence, authors carried out this study to find out whether early iron overload can be detected by echocardiography which is a simple and less expensive tool. The objective of this study was to document echocardiographic changes of cardiac iron overload in patients of thalassemia major even before appearance of symptoms.
Methods: A comparative cohort study conducted from January 2018 to October 2018 in the Department of Paediatrics of SSG Hospital, and Government Medical College, Vadodara. The case group consisted of 35 patients of Thalassemia major. 35 age and sex matched normal children were selected as controls. Relevant blood investigations were performed in cases. 2-Dimensional M-Mode Echocardiography was performed in both patients and controls. Thalassemia major patients were compared to normal healthy children for various parameters in echocardiography indicating the systolic and diastolic function. Proportion and percentage were calculated for descriptive analysis. Independent t-Test was applied between two groups to find out significance level.
Results: For all parameters except End systolic volume and fractional shortening, p values were less than 0.05 which is significant. 85% (30/35) had increase in interventricular septal dimensions (IVSD), 97%(34/35) had increase in posterior wall dimensions (PWD), 82%(29/35) had increased left ventricular internal diameter diastole(LVIDD), 88%(31/35) had increased left ventricular internal diameter systole (LVIDS), 80%(28/35) had increased E/A RATIO .Ejection fraction was affected in 77%(27/35).This shows that patients of thalassemia major have significant cardiac dysfunction; possibly because of cardiac iron overload.
Conclusions: Echocardiography is an effective tool for screening cardiac iron overload in patients of thalassemia major and should be done periodically in all patients.

Keywords: Echocardiography, Left ventricular internal diameter diastole (LVIDD), Posterior wall dimensions (PWD), S. Ferritin, Thalassemia major

INTRODUCTION

The thalassemia's are a heterogeneous group of inherited forms of anaemia caused by mutation that affect the synthesis of hemoglobin. They are a group of genetic disorders of globin chain production in which there is an imbalance between the α-globin and β-globin chain production.[1] β–thalassemia syndromes result from a decrease in β- globin chains, which results in a relative excess of α-globin chain. β–thalassemia major refers to the severe β thalassemia patients who require early transfusion therapy and often is homozygous for β 0 mutation.[2] It is common in central Gujarat due to its high prevalence amongst certain communities.[3,4] Therefore our

hospital has a large follow-up of thalassemia major patients. These patients are usually diagnosed at 6-12 months of age and require life-long blood transfusions at regular intervals.[1,5] However, repeated blood transfusions lead to problem of iron overload in many organs including the liver, pancreas, pituitary gland, skin and heart. The heart has a two-fold risk of dysfunction; one: because of chronic anaemia and resulting hypoxia and two: because of iron deposition.[2] Effects of iron overload can be decreased and possibly reversed by chelation therapy.[6,7]In many developing countries, MRI T2* is used to quantify cardiac and liver iron overload.[1] However, it is not easily available at all centres in India; also, it is very expensive. Echocardiography has been found to be useful as a tool to assess early changes of cardiac dysfunction.[8,9] So, authors carried out this study to find out if cardiac iron overload can be detected in patients of thalassemia major through echocardiography and what are the changes seen.

METHODS

Present study was a comparative cohort study. Cases and controls groups were selected from patients who came for follow up in hematology clinic and OPD of S.S.G. Hospital, Baroda. Sample size was 35 cases (thalassemia major patients) and 35 controls (Non thalassemic healthy children having no underlying cardiac condition or anaemia). Enrolment was done between January to October- 2018 after taking written consent of patients and controls matching inclusion and exclusion criteria. This study was approved by scientific and ethical research committee medical college and SSG Hospital Vadodara.

Inclusion criteria

For cases (group 1)

- All the children of β- thalassemia major who attend the thalassemia clinic and had received more than 10 PCV transfusions.

For control (group 2)

- Age and sex matched children
- Those having no underlying cardiac disease/anaemia
- Patients visiting under 5-clinics or adolescent clinic for routine follow up.

Exclusion criteria

- Patients having underlying cardiac disease (CHD, RHD, myocarditis)
- Patient who have received less than ten transfusions
- HIV positive patients.

After enrolment, data of patients and controls was entered into predesigned proforma. Relevant blood investigations were performed in cases. 2-dimensional M-mode echocardiography was performed in all the patients and controls by a qualified paediatric cardiologist.

Thalassemia major patients were compared to normal healthy children for various parameters in echocardiographic changes. These parameters were: diastolic and systolic pulmonary artery pressure, ventricular septal wall thickness (IVSD), Left ventricular posterior wall thickness (PWD), Left ventricular end-diastolic and end-systolic cavity dimensions. (ESV) and (EDV), Left atrial cavity dimensions, E/A ratio of the mitral valve, ejection fraction (EF), fractional shortening (FS). All these parameters were expressed as Mean±SD. Proportion and percentage was calculated for descriptive analysis. Statistical analysis was carried out using independent T-test between the two groups to find out significance level.

RESULTS

All patients of thalassemia major on regular follow-up at our OPD were taken as group 1 (cases) and age and sex matched non thalassemic, non-anemic children were taken as group 2 (control).

Table 1: Age and sex distribution of patients (thalassemia major).

Age	6 months-5 years	6-10 years	11-18 years	%
Male	5	6	11	62
Female	2	5	6	38
Total	7	11	17	

Total 70 patients were enrolled: 35 cases and 35 controls.

Maximum patients were in the age group of 11-18 years. By this age most of the patients have been properly explained about their disease and are on regular transfusion and follow up (Table1).

The frequency of transfusion for the patients ranged from 15 days to 45 days. Based on this, transfusion requirement was calculated.

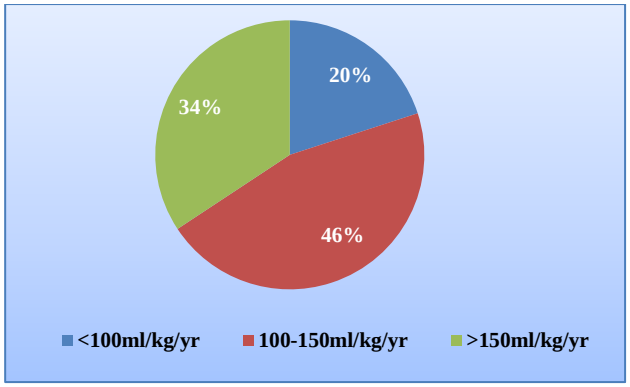

Figure 1: Transfusion requirement.

Majority of patients had transfusion requirement between 100-150ml/kg/year (Figure 1).

Table 2: Echocardiography measurements in thalassemia major patients.

Echocardiography M mode	Mean (N=35)	Median	SD
IVSD (mm)	7.95	8	1.43
PWD (mm)	7.66	7.6	1.27
LVIDD (mm)	39.25	38	6.47
LVIDS (mm)	25.23	25	4.62
EDV (mm)	69.44	63	27.3
ESV (mm)	32.09	25.8	36.4
EF%	62.9	62	6.97
E/A ratio	2.00	2	0.44
FS%	33.74	34.8	5.3

Repeated transfusion leads to iron accumulation in the body which is reflected by serum ferritin levels.

Table 3: Echocardiographic measurements in control group.

Echocardiography M mode	Mean (N=35)	Median	SD
IVSD (mm)	6.77	7	0.60
PWD (mm)	5.91	6	0.28
LVIDD (mm)	32.31	33	2.66
LVIDS (mm)	20.37	21	2.16
EDV (mm)	52.23	49	11.40
ESV (mm)	21.17	22	5.02
EF%	67.49	69	2.44
E/A ratio	1.63	1.7	1.53
FS%	35.6	35.6	2.18

Generally, a serum ferritin level above 1000ng/L is considered as an indication for chelation therapy. A 34% patient had S. ferritin >3000, 54% patient had S. ferritin between 1500-3000 and 11% patient had S. ferritin below 1500 (Table 2). So, all patients had requirement of chelation therapy. Almost all patients were on regular chelation therapy with oral chelator deferasirox. No patient was taking parenteral chelator deferrioxamine.

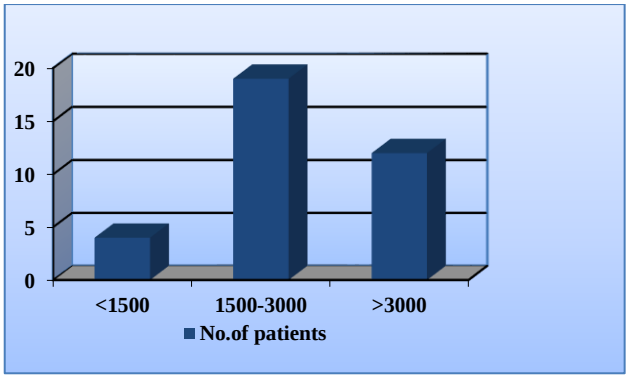

Figure 2: Serum ferritin levels.

Comparison of echocardiographic parameters between cases and controls: (Tables 2, 3 and 4) and Figures 2 and 3.

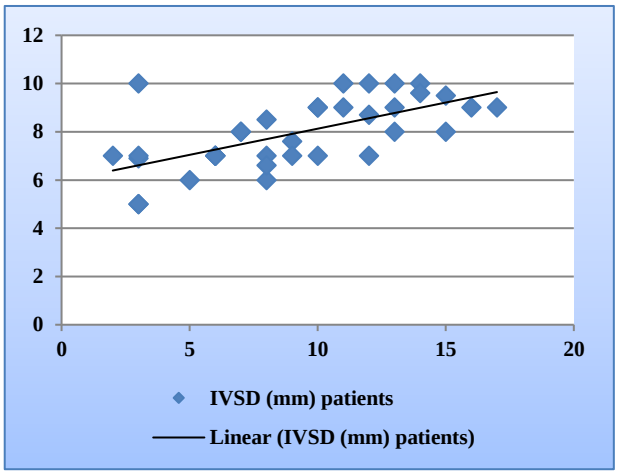

Figure 3: IVSD (mm) patients.

On applying t-test it was found that for all parameters except end systolic volume and fractional shortening, p values were less than 0.05 which are significant. The parameters affected most are Posterior wall thickness and left ventricular internal diameter in systole.

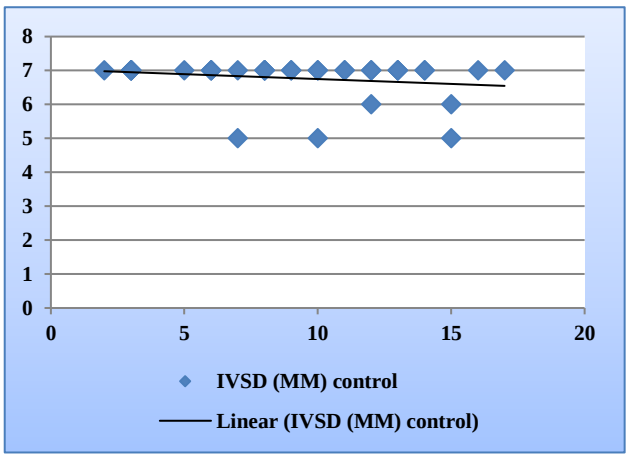

Figure 4: IVSD (mm) control.

So, this suggests that there is left ventricular diastolic dysfunction in patients of thalassemia as compared to control group and this due to iron overload. This echocardiographic pattern of diastolic filling is described as restrictive and is indicative of reduced ventricular chamber compliance.

Table 4: Comparison of echocardiographic measurements in patients with β-thalassemia major and control subjects (Mean±SD).

Echocardiography M mode	B-thalassemia major (N=35) Mean±SD	Control (N=35) Mean±SD	SD	P values
IVSD (mm)	7.95±1.43	6.77±0.60	1.43	<0.00004
PWD (mm)	7.66±.27	5.91±0.28	1.27	<0.00000001
LVIDD (mm)	39.25±6.47	32.31±2.66	6.47	<0.0000004
LVIDS (mm)	25.23±4.62	20.37±2.16	4.62	<0.0000000009
EDV (mm)	69.44±27.3	52.23±11.40	27.3	<0.001
ESV (mm)	32.09±36.4	21.17±5.02	36.4	NS (0.08)
EF%	62.9%±6.97	67.49±2.44	6.97	<0.0006
E/A ratio	2.00±0.44	1.63±1.53	0.44	<0.000002
FS%	33.74%±5.3	35.6±2.18	5.3	NS (0.06)

Table 5: Correlation with S. ferritin levels.

Echocardiography parameters	S. ferritin, <2000 (no=10) Mean±SD	S. ferritin>2000 (no=25) Mean±SD	P values
IVSD (mm)	7.9±1.42	7.98±1.48	0.8 (NS)
PWD (mm)	7.64±1.18	7.67±1.33	0.9 (NS)
LVIDD (mm)	37.4±7.37	40±6.08	0.3 (NS)
LVIDS (mm)	24.9±5.80	25.36±4.19	0.8 (NS)
EDV (mm)	64.48±31.70	71.42±25.85	0.5 (NS)
ESV (mm)	24.42±13.83	35.16±42.11	0.2 (NS)
EF%	63.4±5.76	62.65±7.5	0.7 (NS)
E/A ratio	1.8±0.39	2.08±0.43	0.07 (NS)
FS%	32.2±4.3	34.5±5.7	0.2 (NS)

In present study (30/35) 85% had increase in interventricular septal dimensions(IVSD), 97% (34/35) had increase in posterior wall dimensions (PWD), 82% (29/35) had increased left ventricular internal diameter diastole(LVIDD), 88% (31/35) had increased left ventricular internal diameter systole (LVIDS), 80%(28/35) had increased E/A ratio) early and late diastole caused by atrial contraction,65% (23/35) had effect on ESV, 28% (10/35) had affect FS%, 71% (25/35) had effect on EDV,77%(27/35) had effect on EF%.

There is no major correlation between S. ferritin levels and echocardiographic findings in present study (Table 5).

DISCUSSION

Thalassemia major is a common hematological disorder amongst the pediatric population in the Indian subcontinent, especially in western India.

In tertiary care hospitals like ours these patients are managed by regular blood transfusions. The pre-transfusion hemoglobin of these patients needs to be kept at 9-10g/dl. All patients in present study were on regular blood transfusions: every 15-30 days.

However, authors found that the pre-transfusion haemoglobin of majority of our patients (45%) was between 6-9g/dl. This happens because of limited availability of blood transfusion, patients coming from peripheral areas, poor financial status.

Patients of thalassemia major have iron overload due to the following three reasons: repeated blood transfusions, increased iron absorption from the GI tract, ineffective erythropoiesis.

The most commonly affected organs are liver and heart. Long standing anaemia and resulting hypoxia also contribute to cardiac chamber dilatation and myocardial dysfunction.

Stage I (<100 unit transfused) Stage II (100-400 units transfused) Stage III (>400 units transfused). None of the patients in present study had any obvious signs or symptoms of cardiac dysfunction. However, they had significant myocardial dysfunction on Echocardiography. So, they were in stage I-II at the time of present study.

Cardiac disease in patients with iron overload[1]

A similar study was conducted at Department of Pediatrics, LTMMC and GH, Sion Mumbai in 2015. A 32 transfusion dependent patients of thalassemia major were enrolled, and their echocardiographic assessment was done. It was found that ejection fraction was>60% in all patients. However, diastolic dysfunction and restrictive physiology were found in 59.37% of patients. Most of these patients were on oral deferiprone therapy.[9] Similar findings were noted by Spiritop Pet al, Lupi G et al, Elevendi CM et al and Vecchio C et al, in a study conducted in Italy.[10]

There is no major correlation between S. ferritin levels and echcardiographic findings in present study. A similar study done by Mohammad Reza Khalilian , Department of pediatric cardiology school of medicine, Shahid Beheshti university of medical Sciences Teheran, Iran also shows no correlation between S. ferritin levels and Echo findings.[11] So this shows that S. ferritin alone cannot give an idea about tissue iron overload, chiefly myocardial and liver deposition.

Table 6: Stages of cardiac dysfunction due to iron overload.

Stage I (<100 unit transfused)	Stage II (100-400 units transfused)	Stage III (>400units transfused)
Asymptomatic	Asymptomatic or mild fatigue	Palpitation and/or congestive heart failure
Echocardiogram: slight left ventricular wall thickening	Echocardiogram-left ventricular wall thickening. left ventricular dilatation but normal ejection fraction	Echocardiogram: decreased ejection fraction
Radionuclide cine angiogram-normal	Radionuclide cine angiogram-normal at rest but no increase or fall in ejection fraction with exercise	Radionuclide cine angiogram-normal or decreased ejection fraction at rest but a fall in ejection fraction during exercise
24–hour electrocardiogram-normal	24-hour electrocardiogram-atrial and ventricular premature beats	24-hour electrocardiogram-atrial and ventricular premature beats, often in pairs or runs

Another study done by Siddammanahalli J et al, at Department of Pediatrics, BMRCI, Bangalore in 2015 found that myocardial performance index (MPI) is abnormal at S. Ferritin levels above 1000mcg/ml.[12] Here the study subjects had a mean age of 9.21 years.

A study was carried out at department of cardiology, Antalya research hospital, Turkey by Isa Oner et al.[14] They compared cardiac function by T2*MRI, echocardiography with S. ferritin levels. There was good correlation between S. ferritin levels above 1000ng/ml and cardiac dysfunction. The mean age of patients was 24.5+9 years.

The mean age of our patients was 12.6. Most of the Indian studies have found cardiac changes occurring at early age. All our patients were on regular chelation therapy with oral chelating agent deferasirox. Certain studies have shown a better effect of subcutaneous chelating agent deferroxamine on preventing cardiac iron deposition as compared to oral chelator.[7]

So, a provision can be made to provide deferroxamine to patients once they cross 50 transfusions as early changes of dysfunction appear on Echocardiography.

CONCLUSION

Ventricular diastolic dysfunction occurred in all studied patients of Thalassemia major as compared to normal healthy children. There was no systolic dysfunction and fractional shortening in thalassemia major patients.

Ferritin levels had no correlation with cardiac dysfunction. So, clinicians should not rely on *S. ferritin* values alone for long term monitoring of patients.

Cardiac T2MRI is the investigation of choice to look for iron overload. But many studies show good correlation between cardiac 2D Echo and T2MRI. As T2MRI very costly in resource poor settings Echocardiography can be used in place of MRI.

Echocardiography by an expert cardiologist at least once in a year should be part of standard of care for all thalassemia patients.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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