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Echocardiography Based Study of Diastolic Dysfunction in Children with Asymptomatic Beta-Thalassemia Major and its Correlation with Serum Ferritin

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Abstract: ***This was an observational cross sectional study of 96 Patients at R.G Kar Medical College and Hospital, Kolkata. with diagnosis of β Thalassemia major children aged between 2-12 years between 1st March, 2016 to 28th February, 2017. A control group of 100 normal subjects matched according to age and sex, with the cases were also studied. Patients who fulfil the inclusion and exclusion criteria were enrolled for the study after getting written informed consent. Echocardiography study was done of all the patients for assessment of diastolic function and determined whether it has any correlation with serum ferritin level in asymptomatic β Thalassemia major. It showed 66.67% of children were suffering from diastolic dysfunction, most of them were in grade 1 diastolic dysfunction followed by grade 3 diastolic dysfunction. The grade of diastolic function was correlated to the serum level of ferritin***

Keywords: thalassemia, diastolic dysfunction

1. Introduction

Despite the progress in iron chelation therapy, congestive heart failure due to iron accumulation is still the leading cause of death in β-thalassemia major (TM) patients. [4,5]

Cardiovascular complications of thalassaemia can be in the various forms.

Iron overload in combination with other inflammatory and immunogenetic factors can cause left ventricular systolic dysfunction, dilatation and failure, whereas the sole iron overload may result in left ventricular diastolic dysfunction with myocardial restriction and subsequent pulmonary hypertension and right ventricular dilatation. [6]

Patients with TM may remain asymptomatic and global left ventricular (LV) function may be preserved until late in the disease process. So, early detection of myocardial dysfunction by echocardiography may be useful in the management plan.

However, changes of segmental wall motion – the early sign of myocardial dysfunction in thalassemia patients - may be subtle and could be missed by conventional echocardiographic examination which may remain normal until late stages during the disease process. [7]

Tissue Doppler Imaging (TDI) records regional systolic and diastolic velocities within the myocardium. It allows quantitative measurement of both systolic and diastolic velocities directly from the ventricular myocardium with the determination of the extent of mitral annular displacement in systole and diastole. [8]

So, the aim of this work was to investigate the utility of pulsed wave DTI to detect latent or non-overt cardiac dysfunctions in asymptomatic TM patients and its relation to the iron overload assayed by serum ferritin.

Aims and Objectives

To determine whether there is any correlation exists between serum ferritin level and the severity of diastolic dysfunction among asymptomatic β thalassemia major children.

Inclusion Criteria

Study included asymptomatic TM patients with ejection fraction >55% and a normal resting 12-lead electrocardiogram (ECG). These patients were kept on a regular blood transfusion regimen (every 3-4 weeks) since infancy to maintain pre-transfusion Hb above 7 G/dl and post-transfusion Hb above 10G/dl. They were on long-term chelation therapy for at least one year with daily Deferasirox at the dosage of 30 mg/Kg/day.

Exclusion Criteria

Patients with other cardiovascular disease. Those who developed transfusion associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI) were excluded. All β-thalassemia intermedia, thalassemia minor, sickle cell anaemia, other hemoglobinopathy were excluded.

2. Methods

All β-thalassemia major children diagnosed by Hb electrophoresis without any pre existing cardiovascular disease and receiving regular blood transfusion for more than 2years.

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Diastolic function was seen of all patients by evaluating various parameters.

For the purpose of this study, severity of iron overload was defined by serum level of ferritin:
Group A <2500 ng/mL mild.
Group B 2500 – 5000 ng/mL moderate
Group C >5000 ng/mL severe.

3. Observations

The total number of β Thalassemia major patient in this study conducted at R.G Kar Medical College & Hospital was 96. Among them 55 were male and 41 were female.

Age Distribution
12 cases were in age group 2-4
69 cases were in age group 5-10
15 cases were in age group 11-12

Table 1: Comparison of the PWD and tissue Doppler data in serum ferritin groups

Doppler data	Serum ferritin level		
	<2500 ng/mL (n=33) median (range)	2500–5000 ng/mL (n=39) median (range)	>5000 ng/mL (n=24) median (range)
EF(%)	68 (62-76)	64 (58-76)	60 (56-67)
E (cm/s)	66.90(45.1-90.7)	62.30(35.7-93.6)	68.25(58.4-80.8)
A (cm/s)	67(40.2-147)	97.1(51.8-190)	35.55(27.6-39.2)
E/A	1.11(0.44-1.40)	0.60(0.33-1.23)	1.94(1.68-2.25)
DT(ms)	198(154-274)	256(155-296)	122(110-128)
PVAR-MVA duration (ms)	-28(-36 to -18)	-15(-21 to +36)	35(32 to 38)
E′ (cm/s)	11.30(8.4-12.8)	8.40(5.5-9.7)	4.20(3.5-4.7)
E/E′	6.10(4-7.8)	7.10(4-12.8)	16.15(15.2-17.6)
IVRT (ms)	78(72-94)	95(66-99)	60(55-67)

Table 2: Demographic and clinical characteristics of β thalassemia major patients according to serum l level of ferritin

Demographic and clinical data	Serum ferritin level			Kruskal Wallis Test value	P value
	<2500 ng/mL (n=33) median (range)	2500–5000 ng/mL (n=39) median (range)	>5000 ng/mL (n=24) median (range)		
Age (years)	5(2-9)	8(4-11)	11(9-12)	65.27	<0.05
Height (cm)	102(87-124)	115(94-126)	124(117-135)	57.58	<0.05
Weight (kg)	14(8.4-23)	18(12-23)	22.1(14.5-26)	49.45	<0.05
Pulse (beats/ minute)	87(75-90)	84(78-95)	78(74-86)	29.06	<0.05
Systolic BP (mmHg)	86(80-100)	96(78-104)	102(92-108)	54.73	<0.05
Diastolic BP (mmHg)	50(42-60)	52(44-60)	56(50-64)	19.69	<0.05
Hemoglobin (g/dL)	8(6.8-8.8)	8(6.6-9.1)	7.9(7.6-9)	0.07	0.964
Total transfusion (times/year)	13(10-16)	14(11-16)	17(15-19)	58.65	<0.05
Serum ferritin (ng/ml)	798(560-2020)	2790(2534-3900)	5756(5240-6712)	85.70	<0.05

Cardiac failure due to iron overload remains the most common cause of death in β-TM patients accounting for up to 71% of all deaths from this disease. [94]

The average age of onset of cardiac failure in thalassemia patients was 16 years before initiation of regular transfusion therapy and chelation. [96] However regular transfusion and chelation therapy has increased the age of onset of cardiac failure in thalassemia.

The prevalence of diastolic dysfunction in our study was 66.67%. Diastolic dysfunction on Doppler echocardiography was present in 59.37% patients in a study conducted by C. Chate. [106]

Hankins et al studied 47 patients with transfusion dependant anemias. [107] 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.

Spirito et al studied 32 patients with thalassemia major and found impaired diastolic Doppler indices in patients having normal systolic function. [108]

Echocardiographic evaluation of diastolic functions has been traditionally performed by measurement of trans-mitral flow parameters including the early (E) and late (A) diastolic filling velocities and the E/A ratio with conventional pulsed wave Doppler.

Our findings support the hypothesis that PWD and TDI patterns of diastolic LV dysfunction reflect the severity of iron overload. Diastolic LV dysfunction was absent in all patients with serum ferritin <2500 ng/mL and was present in all patients with serum ferritin >5000 ng/mL. Difference of PVAR – MVA duration and E/Em were significantly increased in the serum ferritin >5000 ng/mL group relative to both of the other groups. DTwas significantly decreased in patients with serum ferritin >5000 ng/mL. These Doppler parameters significantly correlated to the serum ferritin.

The median serum ferritin level was 781.5 ng/ml in patients with normal diastolic function, where as it was 5756ng/ml with grade 3 diastolic dysfunction.

Different patterns of abnormality were documented by other researchers, [100,101] who found a significant reduction in both E and A velocities in TM patients than normal subjects without significant alteration in E/A ratio. Moreover, E/A

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ratio was found to be increased in thalassemia patients in the study done by Garadah et al. [102] denoting restrictive diastolic dysfunction.

In our study E/A ratio was 1.11(median) in serum ferritin level <2500ng/ml and 1.94(median) in serum ferritin level >5000ng/ml group of patients and was not statistically significant.

In terms of diastolic dysfunction indices, the studied TM patients had significantly lower early diastolic velocity E′ and higher IVRT.

Decreased E' is one of the earliest markers of diastolic dysfunction and is present in all stages of diastolic dysfunction. Reduced E' velocity in TM patients was found by Garadah T et al who attributed this to myocardial stiffness.[102]

There was reduced E' velocity with increased serum ferritin level in our study which is also supported by previous studies.

Combining trans-mitral flow velocity with annular velocity (E/E′) has been proposed as a tool for assessing LV filling pressures since it is influenced by both trans-mitral driving pressure and myocardial relaxation. [103] Because E` velocity remains reduced and mitral E velocity increases with higher filling pressure, the ratio between trans-mitral E and E` (E/E` ratio) correlates well with LV filling pressure or pulmonary capillary wedge pressure (PCWP).

The median E/E' ratio were 16.15 in grade 3 DD , 11.60 in grade 2 DD , 6.8 in grade 1 DD and 6.05 in normal diastolic function. It was statistically significant.

Ommen et al. revealed the combined variable of E/Em provided the better estimate of LV filling pressure than other methods.

Silvilaira et al had shown Deceleration time (DT) has a significant correlation with serum ferritin. Difference of pulmonary vein atrial reversal flow and mitral valve A wave duration (PVAR–MVA) and early ventricular filling velocity to early diastolic myocardial velocity ratio (E/Em) significantly correlated with serum ferritin. [105]

In our study DT was <140ms in grade 3DD where as it was >140ms in other grades of DD and was also significant statistically.

The mean PVAR-MVA (ms) were -28ms (no DD), -16ms (grade 1DD), 33ms (grade 2DD) and 35ms (grade 3 DD) respectively and had a linear relationship with serum ferritin level. The value of PVAR-MVA increases with increasing serum ferritin levels.

Diastolic dysfunction generally appears before systolic dysfunction in the natural history of ventricular dysfunction. As there is a linear relationship between serum ferritin level and grade of diastolic dysfunction, with regular use of adequate chelation therapy along with blood transfusion the progression of cardiac dysfunction can be deferred.

4. Conclusions

66.67% of children were suffering from diastolic dysfunction, most of them were in grade 1 diastolic dysfunction followed by grade 3 diastolic dysfunction and there is a linear relationship between serum ferritin level and grade of diastolic dysfunction

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