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A Study on Thalassemic Children to Assess Cardiovascular Changes, In a Rural Medical College Hospital; West Bengal; India

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Abstract: *Thalassemia major is the most common inherited haemolytic anaemia presenting with chronic anaemia and its consequences. Combination of blood transfusion and chelation therapy has prolonged survival in thalassemic children significantly. However this has given rise to increased iron overload and consequent cardiac complications. The present cross-sectional study was contemplated with an aim to assess cardiovascular complications in thalassemic children and its relationship with iron overload.*

Keywords*: Thalassemia; cross sectional study; cardiovascular complications; iron overload, India.*

I. Introduction

Thalassemia is the most common monogenic disorder in the world. It has been said to be traditionally confined to Mediterranean basin, Middle East, North India, Southeast Asia and the Indochina Peninsula. However immigration of population has resulted in more universal distribution of this disease[1]. Therefore currently it is considered a global disease. In India approximately 3-10% of people carry thalassemia gene[2]. Children with thalassemia major presents with a state of chronic anaemia with growth retardation, bone narrow expansion, extramedullary haematopoiesis, splenomegaly , greater intestinal iron absorption and hypercoagulability . Cooley and Lee first described this syndrome in 1925; hence it was termed Cooley's anemia[3].

Worldwide thalassemia carrier state affects more than 250 million persons (carriers) i.e. almost 1.5% of world population. About 100000 children are born every year worldwide with thalassemia major (homozygous state for thalassemia)

In β thalassemia major lack of synthesis of β chain will lead to lack of adult haemoglobin HbA($\alpha 2\beta 2$) and excess fetal haemoglobin, HbF($\alpha 2\gamma 2$), and free α chains which precipitate on the inner surface of RBC membrane causing hemolysis due to reduced deformability of the RBC . The hemolysis in association with increased HbF will cause hypoxia with elevation of erythropoietin level and increased medullary and extramedullary haematopoiesis; resulting in bone expansion and hepatosplenomegaly.

Regular blood transfusion to maintain Hb% at an optimum level (pretransfusion level at 9-10.5 gm/dl and post transfusion level not more than 15gm/dl) remains the mainstay of treatment of thalassemia major[4]. However regular transfusion will invariably lead to iron overload because each millilitre (ml) of RBC contains about 1.16mg of iron. Thus if 100-200 ml of pure RBC per kg are transfused per year it will create an iron overload of 116-232 mg/kg/year [5].

The excess iron which is unbound (non-transferrin-bound –iron –NTBI) is able to redox cycle between Fe+2 and Fe+3 and can generate reactive oxygen species (ROS) which will culminate in cell death. The damage involves practically all organs of the body viz. spleen, liver, bone narrow, endocrine glands and finally myocardium[6]. Myocardial iron deposition is the trigger for development of heart failure. Spectrum of myocardial involvement include left ventricular systolic dysfunction, dilatation, failure, pulmonary hypertension and right ventricular dilatation. Both dilated and restrictive cardiomyopathy has been described in literature[7]. Vascular involvement has recently been described in literature in a study by Cheung YE et al in 2002. Increased arterial stiffness along with defective NO-dependent vasodilatation was demonstrated in 30 patients without evident cardiac disease[8].Increased arterial stiffness will lead to impaired left ventricular performance (left ventricular after load mismatch)[9,10].

Iron overload can be assessed by serum ferritin level; however myocardial iron overload can be accurately measured by MR T2 relaxation time[11]. As T2 relaxation time is reduced below 20ms (milliseconds) it reliably predicts the risk of decline in systolic ejection fraction[11,12].

Standard treatment of iron overload comprises of Deferoxamine, Deferiprone and Deferasirox, the first agent used subcutaneously and the next two drugs are available orally. Often combined chelation therapy is preferred.

In β thalassemia major cardiomyopathy is most commonly the terminal event leading to death and it is well documented that planning early and effective chelation program in thalassemia will definitely go a long way in preventing , at least delaying cardiac complications[13].

Lower ferritin levels are associated with lower prevalence of cardiac complications and increased survival[14, 15].

Patients having values less than 2500ng/dL on two third occasions had less risk of cardiac complications than the patients with level greater than 2500ng/dL[16]. We therefore contemplated the present study with the aim to assess incidence of cardiovascular complications in patients with β thalassemia major and to evaluate its relationship with serum ferritin levels.

II. Aims and objectives of the study

The consequences of thalassemia major affect virtually every organ system. Cardiac complications are the commonest cause of mortality and one of the major causes of morbidity. Iron overload causes permanent cardiac damage.

The present study was directed with the objectives:

1. To study different cardiovascular changes in β thalassemia major patients.
2. To evaluate the relationship of serum ferritin level and cardiac complications

III. Materials and methods

The present prospective study was conducted in the Department of Paediatric Medicine; Bankura Sammilani Medical College, Bankura, West Bengal; India. All the thalassemic children up to the age of twelve years admitted in the department of Paediatric Medicine from 1st June 2014 to 31st May 2015 comprised the study material.

A total of one hundred (100) patients participated in the study. A detailed medical history including history of first blood transfusion and complete transfusion history including any chelation therapy was taken. Complete general clinical and cardilogical examination was done using a predesigned proforma.

Investigations undertaken were complete hemogram, chest x-ray P-A view, ECG – 12 leads, echocardiography and serum ferritin level.

Having obtained ethical clearance from the Institutional Ethics Committee the study was conducted after getting written consent from the parents/ guardian. All the children recruited in the study were examined and investigated for any cardiac complications. Special stress was given on transfusion history and history of cheletion therapy. Pretransfusion haemoglobin level and serum ferritin level was estimated. Chest x-ray was done in the department of radiology and ECG and echocardigraphy was done in the department of cardiology. Echo with Doppler study was done with Siemens Acuson CV 70 echocardigraphy machine. Data analysis was done by IBM SPSS statistics V 20 software. Study of significance was analysed by chi-square test for qualitative data and student t-test for quantitative data. P value <0.05 was considered to be significant

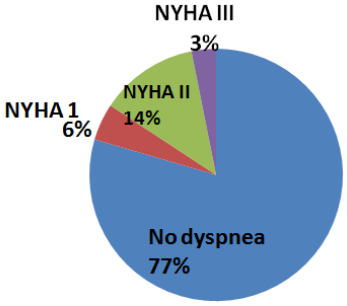
IV. Results and analysis

Among total 100 children included in the study 56(56%;n=100) were boys and 44(44%;n=100) were girls. Mean age of the patients was 8 $\pm$2.5 years. The youngest patient was 1 year 8 month old and the oldest was 12 years old.

Table1: cardiovascular symptoms and signs in the study population (n=100)

Symptoms and Signs	Number
Fatigue	53
Dyspnea	23
Palpitation	15
Chest pain	7
Edema	24
Cyanosis	3
Ejection systolic murmur	41
CHF	27
PAH	6

Figure 1: -Pie diagram showing NYHA dyspnoea grades among the study populations



Among 100 thalassemic children 77 cases did not have any dyspnea, 6 children presented with NYHA grade I, 14 children with NYHA grade II and 3 children with NYHA III

In this study mean age of first blood transfusion was 11.37 ±6.9 months. Maximum age of first transfusion was 27 months and minimum age was 3 months

Table-2: Showing number of thalassemia children on chelation therapy (Tab.Deferasirox)

Chelation therapy	Boy	Girl	Total
Taking	34	28	62
Not taking	22	16	38

Out of 100 thalassemia children total 62 were taking chelation therapy. Among them 34 were boys and 28 were girls. 22 boys and 16 girls, total 38 children were not taking any chelating medications.

Table -3: Showing serum ferritin levels in study population

<1000 ng/dL	6
1000-2500 ng/dL	59
>2500 ng/dL	35

The mean value of serum ferritin in the study population was **2227.26 ± 1350.4ng/dL.** There were 6 cases with serum ferritin level below 1000ng/dl and 35 cases with more than 2500ng/dl serum ferritin. There were 59 cases with serum feritin levels between 1000-2500ng/dl. Chest x-ray reveled cardiomegaly in 30 patients (30%;n=100) and ECG showed LVH in 26 patients (26%;n-100)

Table -4: Showing comparative cardiovascular findings between two groups according to serum ferritin levels (<2500ng/dl and >2500ng/dl)

	Ferritin<2500ng/dl	Ferritin>2500ng/dl	P value
Mean age(year)	7.6+2.7	8.75 +2	**0.048**
Ethnicity	Tribal -13 Non tribal -52	Tribal -8 Non tribal -27	0.799
Pulse	101.9 ± 14.1	119.46 ± 18.9	<0.001
Systolic BP	111.48 ± 10.86	109.69± 8.09	0.395
Diastolic BP	70.69± 8.5	71.66± 6.9	**0.568**
Fatigue	23	30	<0.001
Dyspnea	3	20	<0.001
Palpitation	3	12	<0.001
Chest pain	1	6	0.007
Edema	5	19	<0.001
Cyanosis	2	1	**0.720**
ESM	18	23	0.002
CHF	7	20	<0.001
PAH	1	5	0.019
CXR- Cardiomegaly	8	22	<0.001
ECG – LVH	3	23	<0.001
Haemoglobin (gm%)	5.4 ± 1.6	4.46 ± 1.26	0.002
Chelating agent taken	52	10	<0.001

ESM= Ejection systolic murmur, CHF=Congestive heart failure, PAH=Pulmonary arterial hypertension , ECG= Electrocardiography , LVH=Left Ventricular Hypertrophy

Table 4 shows that all the cardiovascular findings are present more frequently in thalassemic children with serum ferritin >2500ng/dl and in a statistically significant manner.In lower serum ferritin group more patients are on chelation therapy and the difference is statistically significant.

Table -5: Showing comparative echocardiography findings between two groups according to serum ferritin levels (<2500ng/dl and>2500ng/dl)

	Ferritin <2500ng/dl n=65	Ferritin >2500ng/dl n=35	P value
EF(%)	69.38 ± 6.87	62.25± 6.67	<0.001
LVPWT (mm)	5.37 ± 1.06	8.63 ± 3.4	<0.001
IVWT (mm)	5.43 ± 1	9.37 ± 3.09	<0.001
LVEDD (cm)	4.75 ± 0.83	3.89± 1.25	<0.001
E/A Ratio	1.31 ± 0.46	2 ± 0.93	<0.001

EF =ejection fraction, LVPWT = Left ventricular posterior wall thickness, IVWT = Interventricular wall thickness, LVEDD = Left ventricular end diastolic dimension , E/A ratio = ratio of peak flow velocity of LV inflow in early diastole(E) and late diastole with atrial contraction(A)

Echocardiography parameters which define the left ventricular functional capacity were taken for this study. Mean values of each parameter in each group were calculated. Ejection fraction had higher mean value in lower ferritin group and difference was statistically significant (p<0.001). The mean value of left ventricular posterior wall thickness was more in higher ferritin group with statistical significance (p value<0.001). The mean value of interventricular wall thickness was more in higher ferritin group with statistical significance (p<0.001). Left ventricular end diastolic dimension had a lower mean value in higher ferritin group and it was also statistically significant (p value <0.001). The mean value of E/A ratio was higher in higher ferritin group with statistical significance (p<0.001).

Table - 6: Showing comparative echocardiography findings between two groups according to serum ferritin levels (<2500ng/dl and >2500ng/dl)

	Ferritin <2500ng/dl	Ferritin >2500ng/dl
Dialated Cardiomyopathy	8	4
Restrictive Cardiomyopathy	0	17
Normal CVS	57	14

Echocardiography findings were divided into two groups: children with <2500ng/dl serum ferritin and children with>2500ng/dl serum ferritin levels. Out of total 65 cases in the group of lower ferritin levels, 57 cases were with normal echocardiography findings. Out of total 35 cases in the group with higher ferritin levels, there were 14 cases with normal findings. In study groups with<2500ng/dl serum ferritin levels 8 cases had dilated cardiomyopathy. There was no restrictive cardiomyopathy cases in this group. Study group with >2500ng/dl serum ferritin had 4 cases with dilated cardiomyopathy and 17 cases with restrictive cardiomyopathy.

V. Discussion

In the present study thalassemia patients who are transfusion – dependent had cardiovascular complications. In this study out of 100 children 27 cases presented with signs and symptoms of heart failure. In chest x-ray there was cardiomegaly in 30 cases. These findings are similar to findings in other study (Khan FR et al -2006)[17].

Pulmonary hypertension was found in 6 cases; 5 of which had serum ferritin level >2500ng/dl. This finding is also consistent with previous studies.[18, 19].

Out of 100 children recruited in the present study 65 were receiving chelating agents regularly (Tab deferasirox). In our centre Deferasirox is supplied to thalassemia children with serum ferritin above 1000ng/dl. Other studies however document less percentage of patients receiving oral chelating agents[20]. Early detection of myocardial siderosis by cardiac MR imaging and intensification of chelation programme has shown marked improvement in survival and cardiac function[21].

Echocardiography findings in our study reveals no systolic dysfunction (Ejection fraction in all patient >50%), this finding being consistent with previous study[20, 22].

Dilated cardiomyopathy developed in 12 cases and restrictive cardiomyopathy in 17 cases. 8 patients with dilated cardimyopathy had serum ferritin level <2500ng/dl and 4 had level >2500ng/dl. All the 17 cases with restrictive cardiomyopathy had serum Ferritin >2500ng/dl.

Mean serum Ferritin in this study was 2227.26 ± 1350.4ng/dl. 6 cases were having ferritin <1000ng/dl: 59 cases had ferritin level in the range of 1000-2500ng/dl: and 35 cases had the level >2500ng/dl.

Almost all the cardiovascular complications were found to be higher in the high-ferritin group (serum ferritin >2500ng/dl) than in low-ferritin group (serum ferritin <2500ng/dl) and the association was statistically significant (P value<0.05)

It was found that 52 cases (80%) were taking regular chelation therapy in low ferritin group. Whereas 10 cases (28.5%) were on chelation therapy in high ferritin group. So it is obvious that chelating agents definitely reduce serum ferritin level and reduce cardiovascular complications.

VI. Conclusion

This study helps us to know the pattern of cardiovascular complications in thalassemia major children in a Rural Medical College Hospital; West Bengal; India. It also reveals the association of cardiovascular complications with serum ferritin level.

VII. Contribution

Dr. Mukherjee actually planned and conducted the study under guidance and supervision of Dr. Pal. Dr. Mukherjee also performed the statistical analysis.
DR. Pal drafted the final manuscript and added important intellectual contents.
Dr. Sinha helped actively during the entire duration of study. She also added some intellectual contents.
Dr. Banddyopahaya also provided active assistance during the course of the study. He helped in compilation of the data.
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