

Original Research Article

Serum ferritin levels and its correlation with cardiac iron overload with the help of cardiac T2* magnetic resonance imaging

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ABSTRACT

Background: Frequent blood transfusions in thalassemia major is associated with iron overload in these patients. To reduce the mortality and morbidity, proper usage of iron chelators is necessary to treat iron overload. Cardiac magnetic resonance imaging (MRI) guides in quantification of iron overload in heart. The purpose of this study is to see the correlation between serum ferritin level and T2* MRI in patients with beta thalassemia major.

Methods: Period of the study is September 2018 to September 2020. Total 25 patients diagnosed with β -thalassemia major above 5 years of age were enrolled in the study. They were on regular transfusions. Cardiac T2* MRI was done in these patients and correlated with serum ferritin levels.

Results: There was no significant correlation observed between cardiac T2* MRI and serum ferritin values ($p=0.66$, $r=-0.094$).

Conclusions: Our results showed no significant correlation between serum ferritin and cardiac T2* MRI values. Ferritin alone cannot be used as index of myocardial iron overload in thalassemia major.

Keywords: Iron chelators, Iron overload, Serum ferritin, T2* MRI

INTRODUCTION

Thalassemia major is the most common hemolytic disorder in India. Globally, it is estimated that there are 270 million carriers with haemoglobinopathies, out of them 80 million are carriers of β -thalassemia. It is predicted that in next 20 years about 90000 patients will be born in the world, 95% of them will be in Asia specially in India and middle east.¹ The frequency of β -thalassemia in this Sindhi population group is 15-17%.² In Maharashtra, there is a small migrant population from Sindh in Pakistan. Mortality and morbidity associated with this disease is quite high.

As hemolysis progress, severe anemia develops leading to increased intestinal iron absorption and requirement of frequent blood transfusions to maintain hemoglobin. As the blood transfusions are the mainstay of treatment. A common clinical problem in these patients treated with blood transfusion is iron overload in different organs such as liver, heart, endocrine glands and other organs. Iron induced cardiotoxicity remains a leading cause of morbidity and mortality in thalassemia major children.³ Cardiac hemochromatosis causes a dilated cardiomyopathy with dilated ventricles, low left ventricular ejection fraction (LVEF), and decreased fractional shortening leading to heart failure.⁴ Once heart failure develops, the prognosis is poor.

This iron overload is cleared to some extent with the help of iron chelators. Appropriate usage of these drugs needs an accurate measurement of iron levels. MRI offers a non-invasive imaging study for assessment of tissue iron levels, used to monitor iron load in the heart so that patients at risk for cardiac and liver failure can potentially be identified before lethal symptoms develop. In comparison to standard monotherapy with deferoxamine, combination treatment with additional deferiprone has reduced myocardial iron and improved the ejection fraction and endothelial function in patients with thalassemia major with mild to moderate cardiac iron loading.⁵ Early T2* sequence imaging detects cardiac iron overload and helps in guiding the chelation therapy, thereby reducing the morbidity of children suffering from thalassemia major.⁶

The present study is conducted to know the correlation of T2* MRI in detecting myocardial iron overload with the serum ferritin levels. Thereby, helping in escalation of chelator therapy when needed, which helps in reducing morbidity and mortality in thalassemia major children.

METHODS

This is a cross sectional study conducted in department of pediatrics, Dr. D. Y. Patil medical college, hospital and research center, Pimpri, Pune for a period of 2 years between September 2018-September 2020. 25 diagnosed β -thalassemia major patients were enrolled in this study who were on regular blood transfusions. Thalassemia major patients under age group 8-8 years, who are on repeated blood transfusion 10 times per year for 5 years were included. And excluding criteria are thalassemia trait, minor and intermedia patients. Thalassemia patients under 8 years of age and above 18 years of age.

Informed consent

The purpose of the study and details of protocols were discussed with the parents of patients who were selected by the inclusion criteria. An informed written consent was taken, along with assent from the adolescents.

Ethical clearance of the study was obtained by the institutional ethical committee.

Methodology

A pre-tested, semi structured questionnaire developed and used for data collection. Detail history of all the selected patients along with serum ferritin levels during last 3 months, hemogram values and T2* MRI results were recorded in a questionnaire. The sampling was performed on the basis of simple random method.

Serum ferritin estimation

About 3 ml of patient's blood sample was collected by a clean venepuncture. Serum was separated and stored at-

20°C. Ferritin levels were performed by using indirect enzyme linked immunosorbent assay (ELISA) kit (Orgentec, Germany) along with normal and abnormal controls. Antihuman-ferritin antibodies were bound to microwells.

3-Tesla MRI

Three tesla MRI (Siemens magnetom vida) was used to collect T2* values. Surface coil was used to broadcast and to receive the radiofrequency signals. Respiratory and heart movements were monitored using respiratory sensor and electrocardiography and images in deep inspiration were auto clicked. Motion artifacts were suppressed by spatial pre-saturation slabs. Also, patient is asked to breath hold for few seconds (5-6 seconds). A homogeneous full-thickness ROI was chosen in the ventricular septum. Gradient echo sequence was used to scan heart; slice thickness 8 mm (H), echo time 5, repetition time 1000 ms, flip angle 90°, base resolution matrix 512 pixels, field of view 10×15 cm, and sampling band width-125 kHz. One of the patient MRI is shown in the Figure 1.

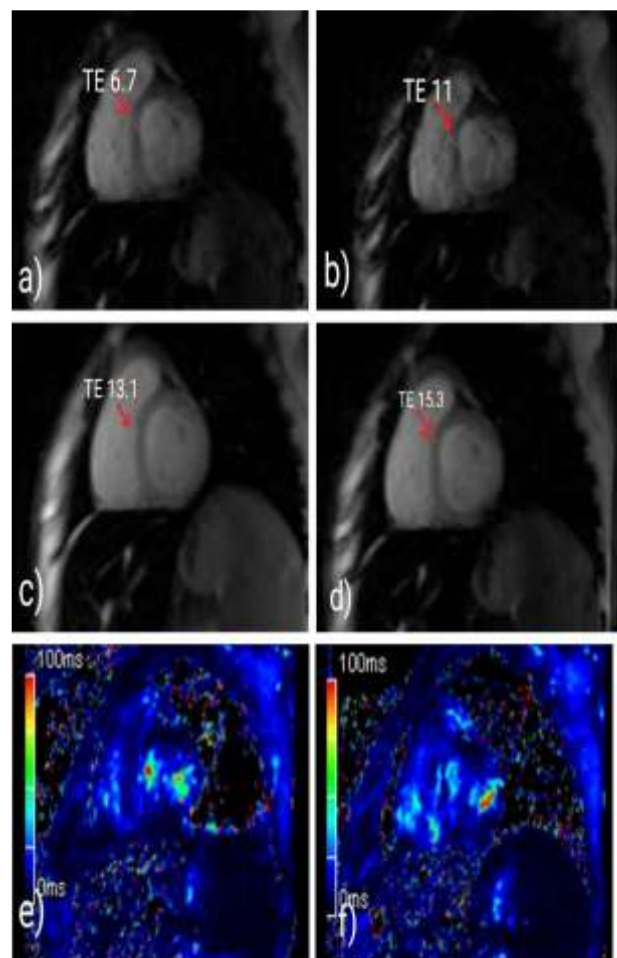


Figure 1: T2* MRI of a patient: (a-d) Two chamber view GRE images of TE values of 2.5, 4.6, 6.7, 8.9. (e and f) These areas are confirmed on T2*.

Data analysis was done using the SPSS (Statistical package for the social science) version 23 for window. The demographic variables, no of transfusion, Sr. ferritin level, MRI values were calculated with no and percentage. The ANOVA test and paired t test was used to find significant difference of Sr. ferritin level and MRI values. Correlation and test for correlation was used to find the significant correlation between Sr. ferritin level, number of transfusions. Quantitative data will be summarized using mean and SD. A probability value of 0.005 was accepted as the level of statistical significance.

RESULTS

The study was performed on 25 patients with beta thalassemia major (64 % male and 36% female). The mean of age of patients was 10.72 ± 2.01 years and its range were 5 to 18 shown in Figure 3. It was observed that 64% subjects were boys and 36% were girls with male: female ratio of 1.77:1 as shown in Figure 4. Hemoglobin values ranged from 3.8 to 9.1 before transfusion. Mean level of hemoglobin was 6.1 (mg/dl) before transfusion. Average number of blood transfusions were 115.8 (75-160). The mean of serum ferritin level was 3920.5 ng/dl (2000-8852 ng /dl). The mean of cardiac T2* was 24.68 ± 13.33 ms (6-63.0 ms). Three patients underwent splenectomy. The 17 children had short stature. 5 children were not using any iron chelators and rest all patients are on Desirox at various doses. Cardiac T2*MRI is shown in Table 1. Serum ferritin levels are shown in Table 2. No statistically significant correlation was observed between cardiac T2*MRI and serum ferritin ($p=0.66$, $r=-0.094$), as shown in Table 3. Statistically significant correlation was seen between age and number of blood transfusions with $p<0.00001$, shown in Table 4.

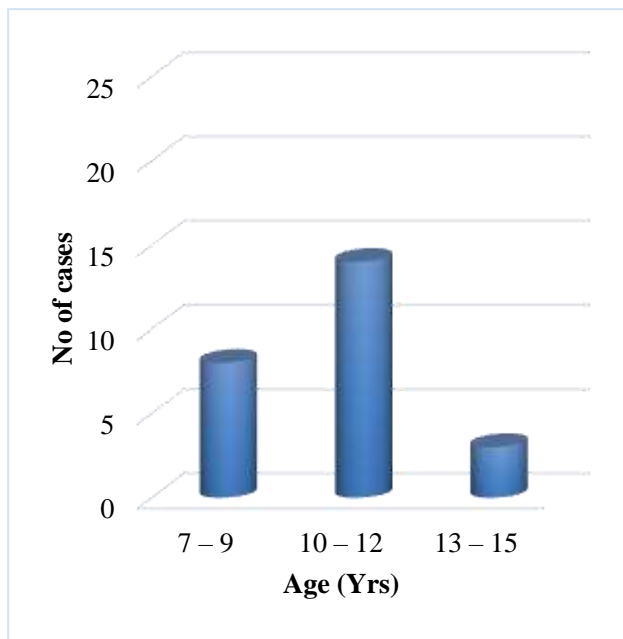


Figure 2: Distribution of cases according to the age.

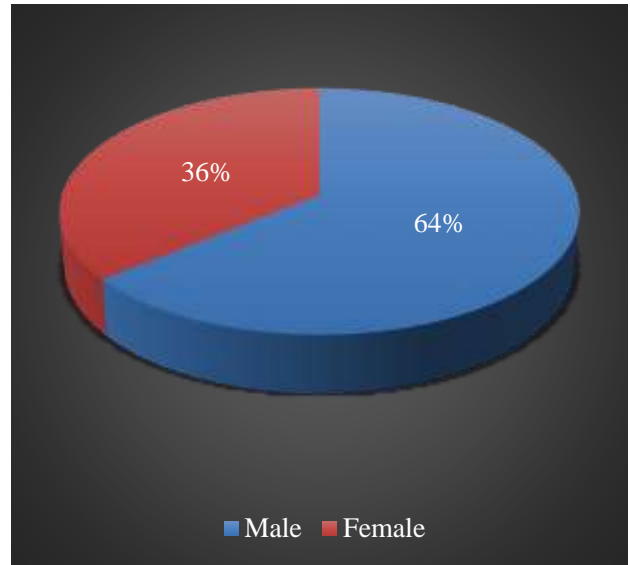


Figure 3: Distribution of cases according to gender.

Table 1: Distribution of cases according to cardiac t2* MRI values.

Cardiac T2* MRI value	No. of cases	Percentage (%)
Normal	8	32
Marginal	7	28
Mild	5	20
Moderate	4	16
Severe	1	4
Total	25	100

Mean=24.68, SD=13.33.

Table 2: Distribution of cases according to serum ferritin levels.

Serum ferritin level (ng/ml)	No. of cases	Percentage (%)
<2000	0	0
2000-4000	17	68
4001-6000	4	16
>6000	4	16
Total	25	100

Mean=3920.56, SD=1816.181.

Table 3: Correlation between cardiac T2* MRI and serum ferritin levels.

Correlation between	R value	P value
Cardiac T2* MRI Serum ferritin	-0.094	0.66

Table 4: Correlation between age of patients and their cardiac T2* MRI values.

Correlation between	R value	P value
Age (years) T2 MRI	0.27	0.20

DISCUSSION

In study, 25 patients of thalassemia major were enrolled who underwent cardiac MRI and estimation of serum ferritin levels. Furthermore, some other variables such as haemoglobin level, transfusion rate type and dose of chelators, demographic variables including age, gender, and anthropometry were also analysed in this study.

It was seen that majority of the patients enrolled in the study were between 10-12 years of age (56%) followed by 7-9 years (32%) with mean age of 10.72 years. It was observed that 64% subjects were boys and 36% were girls with male: female ratio of 1.77:1.

It was observed that mean ferritin levels of these patients was 3920.56 ng/ml and none of the child had serum ferritin levels below 1000 ng/ml. Nadeem Ikran et al in their study observed that 76% patients had values above 2500 ng/ml, with a mean of 3390 ng/ml. 21.34% patients had serum ferritin between 1000 to 2500 ng/ml.⁷ Choudhry VP et al in India reported mean serum ferritin levels to be 6723 ng/ml which was more higher than my study.⁸ Higher ferritin levels are due to inappropriate usage of iron chelators due to high cost and most of the families in this study belongs to below poverty line, and most of the parents were uneducated, have no knowledge of iron chelators. Study conducted by Borgna-pignatti in 2004 showed that serum ferritin values of 1000 ng/ml are associated with decreased mortality and many clinical advantages.⁹

In this study, it is observed that only one (four%) child had severe cardiac iron overload with T2* MRI value of 6 ms with MIC of 3.22 mg/gm of myocardium. Four (16%) had moderate iron overload, 5 (20%) had mild overload, whereas eight (32%) had no iron overload. Patients have categorised a marginal group whose T2* MRI values were ranging between 20-25 ms, who are at risk of entering into mild iron overload group. They require more extensive chelation and more frequent monitoring to avoid further complications. Observed that seven (28%) had marginal iron overload. Out of all children, 60% children had a normal heart with not significant iron deposition, rest all other had some degree of iron deposition posing them to future cardiac risk.

Wahidiyat et al conducted similar study in 162 children of which 85% of children had normal heart with no iron overload.¹⁰ Chaosuwannakit et al also conducted similar study which showed 81.4% children with normal cardiac MRI values, this was conducted in north eastern Thailand among 210 cases.¹¹ Difference in results between studies might be due to limited no. of sample size of this study.

In this study, less than 2 SD defined as short stature and 17 patient (68%) are falling under short stature. This result was similar to previous studies, Vogiatzi et al found 25% were of short stature (height z-score < 2).¹² Hashemi et al also found 65.71% of thalassaemic patients

had height less than fifth percentile.¹³ However these results indicate inadequate transfusions, poor nutritional support and inadequate chelation, explaining the need to increase the awareness of the above.

It was observed that there is significant positive correlation between the age and number of transfusions, which explains that as age increases, need for transfusions also increases. It could be because of splenomegaly, increased destruction of red blood cells, thereby increasing iron deposition in the body. Shah et al conducted a study which also showed similar studies that there was a linear correlation age between and number of transfusions.¹⁴ In contrary to general dictum, the serum ferritin increases as age increases, it was observed that patient with younger age had higher ferritin levels but no significant correlation was established. Bandyopadhyay et al. conducted a similar study which also showed that patients in younger age group had higher ferritin levels. These differences could be due to inappropriate chelation regimens.¹⁵

There was no statistically significant correlation present between serum ferritin levels and T2* MRI values in this study with $r = -0.094$ and $p = 0.64$. Fahmy et al in 2015 conducted a study in which he could not correlate between serum ferritin and T2* MRI values with $r = -0.077$ and $p = 0.528$.¹⁶ Eghbali et al in 2014 conducted a study with $r = 0.120$ and $p = 0.361$ could not able to establish the correlation between these two.¹⁷ Similar to this study, most of the studies failed to correlate serum ferritin level and T2* MRI heart. Only one study conducted in 2015 by Majd et al was able to show some negative correlation between these two values with a $p = 0.002$ and $r = -0.329$.¹⁸ These differences between the studies could be because of different sample size and timing of ferritin levels, use of iron chelators. In this study a single ferritin level was taken 10 days before doing MRI scan, whereas Majd took a mean serum ferritin level over a period of one year repeating every 2 months. In this study a child with 8000 ng/ml serum ferritin level showed no cardiac iron overload whereas child with serum ferritin of 2000 ng/ml had moderate iron overload, hence this shows the importance of cardiac MRI for evaluating iron overload in myocardium. Hence rather than depending on only serum ferritin levels, cardiac MRI should be considered as a primary mode of evaluation for cardiac iron deposition in thalassemia children. Proper chelation techniques which include proper cardiac iron chelator (deferrioxamine) in proper dosages is required.

So, this study highlights early detection of iron overload with the help of cardiac T2* MRI, thereby guiding the proper chelation therapy. This will reduce the overall morbidity and mortality children with thalassemia major.

Limitations

A small sample size and single centre study limits its generalizability. Breath holding by the younger children

for cardiac MRI was difficult, requiring multiple trials for cardiac MRI. Evaluation of the clinical course and follow up with cardiac MRI after treatment was not done as this a cross sectional study.

CONCLUSIONS

No correlation between serum ferritin levels and cardiac MRI values was found, hence monitoring serum ferritin levels is not a suitable method to depict the cardiac status of iron overload. Cardiac T2* MRI is a better way to quantify iron deposition in myocardium. Thereby it will help to guide use of proper chelation therapy and reduce the cardiac complications. Counselling and emphasis have to be done for monitoring of cardiac iron overload with the help of cardiac MRI

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