Original article:

Study of iron overdose in thalassemia major: comparative analysis of magnetic resonance imaging, serum ferritin and iron content of liver and heart

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Abstract

Introduction: As transfusional therapy is the mainstay of treatment, transfusional hemosiderosis has become the major cause of late morbidity and mortality. Ferritin is the principal iron storage protein, found in the liver, spleen, bone marrow, and to a small extent in the blood (serum ferritin-SF). Therefore in this study we compared heart and liver iron concentration with mean ferritin values, to plan a study on iron overdose in thalassemia major patients.

Material and Methods: This was a descriptive and retrospective study in a group of thalassemia major patients, conducted at regional blood centre, Thane, Mumbai in a 2 months duration.IEC approval was received for this study from our IEC. This study project was approved by Indian Council Of Medical Research (ICMR), Delhi. Type of sampling was simple random and 40 patients were analyzed for iron overload by direct method and indirect method.

Result: Liver MRI showed hepatic loading normal in 8(20%) patients, mild in 16(40%) patient, moderate in 11(27%) patients and severe in 5(13%) patient. Heart MRI showed cardiac loading normal in 26(65%) patients, mild in 6(15%) patient, moderate in 4(10%) patients and severe in 4(10%) patient. The mean serum ferritin was 3109.12 238.94 ng/dl, which is markedly higher than the recommended levels for normal individuals.

Conclusion: No correlation was seen between ferritin and cardiac iron storage. However, serum ferritin level is a reliable indicator to evaluate the liver iron level

Keywords: Ferritin , MRI

INTRODUCTION

It is estimated that 1.5% of the world population (3.3% in India), i.e., 200 million people are carriers of the Beta-thalassemia gene. This disease is the most common genetic diseases in the world (1, 2). It is predicted that in the next 20 years, about 900,000 patients with thalassemia will be born in the world, 95% of them will be in Asia especially in India and Middle east (3).Thalassemia involves mainly the under-developed countries and the prevalence of the disease is less in the Europe and North America (4,5) .β-Thalassemia major is a hereditary anaemia characterized by ineffective erythropoiesis and haemolysis (6). The underlying mechanism is defective production of haemoglobin β- chains, resulting in excess of α-chains, which are unstable and precipitate to form intracellular inclusion bodies (7, 8). This excessive intracellular deposition of α-chain material is responsible for accelerated apoptosis of the erythroid precursors and for peripheral haemolysis of the erythrocytes (8). By the age of 3 months, severe anaemia develops leading to increased intestinal iron absorption. To maintain haemoglobin at a level of 10–12 g/dl, patients suffering from β-thalassaemia major need to be given repeated blood transfusions (6). As transfusional therapy is the mainstay of treatment, transfusional hemosiderosis has

now become the major cause of late morbidity and mortality in them. The effective management of patients, and especially of children, with thalassaemia requires optimal monitoring of the toxic effects of both iron overload and excessive chelation therapy. The effects of treatment depends primarily on patient adherence and can be evaluated by determining iron loading by direct or indirect methods. The measurement of iron is important for prognosis and monitoring chelation. Ferritin is the principal iron storage protein, found in the liver, spleen, bone marrow, and to a small extent in the blood (serum ferritin-SF). In majority of the clinical centres, the standard method of evaluating the total amount of body iron is the measurement of the SF concentration in the blood. Serum ferritin has been widely used as a surrogate marker and a target ferritin level of 1,000 μg/l is generally recommended (9,10) . However, serum ferritin represents only 1% of the total iron pool, and as an acutephase protein it is not specific because the levels can be raised in inflammation (e.g. hepatitis) and liver damage (9,11,12). Also, the potential variations of serum ferritin levels create uncertainty regarding its significance, while the discomfort and risk of the direct procedure precludes its frequent use in serial observations. Therefore, the correlation between SF and body iron is not sufficiently precise to be of high prognostic value, especially when associated with inflammation or tissue damage. But serial ferritin measurements are predictive of complications like iron induced heart disease. MRI measure iron concentration indirectly via the detection of the paramagnetic influences of the proton resonance behaviour of tissue water.MRI remains the only non invasive modality in clinical use with the ability to detect cardiac iron levels. Measurement of liver iron by MRI is the best, because it allows an anatomical view of iron overload in the liver. In view of the above mentioned facts it was decided to plan a study on iron overdose in thalassemia major patients.

AIMS AND OBJECTIVES

1. To quantify heart and liver iron concentration by magnetic resonance in multitransfused thalassemia patients.
2. To compare heart and liver iron concentration with mean ferritin values.
3. To classify patients for risk of illness on the basis of level of irons in heart and liver.

METHODOLOGY

A descriptive and retrospective study in a group of thalassemia major patients, followed at regional blood centre .In order to contribute to the general understanding of iron overload in thalassemia major, 40 patients will be analyzed for iron overload by direct method: serum ferritin and indirect method: MRI (for vital organs-heart and liver).T2* MRI is used to assess heart and liver iron concentration, MRI provides a non-invasive method to measure tissue iron concentration. All procedures will be carried out with patient's consent and confidentiality of data will be maintained.

INCLUSION CRITERIA:

1. Records of all the patients who have received transfusional therapy and underwent MRI and serum ferritin evaluation.
2. Records of all thalassemic patients of either gender.
3. Records of all patients 5 years and above.
4. All completed records of the patients.

EXCLUSION CRITERIA

1. Incomplete records.
2. Records with anyone investigation.

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3. Records of patients with history of severe anaemia or any chronic illness.
4. Records of patients with chronic drug intake for any other illness.

STUDY DURATION: Two months

SAMPLE SIZE: 40 patients

STATISTICAL DATA:

We collected the said data, tabulated and analysed to determine correlation between different parameters namely age, sex, serum ferritin level and magnetic resonance imaging of heart and liver.

The identity of patients involved in the study was bounded in strict confidence.

OBSERVATIONS AND RESULTS

40 patients, 19 women (45%) and 22 men (55%) were involved in the study. Table 1 gives a detailed report of iron content and MRI evaluation of liver and heart, as well as serum ferritin level.

- The patient's mean ± SD age was 18.55±6.7 years
- The patient's mean ± SD serum ferritin level was 3109.12±2386.94 ng/mL.
- The mean ± SD relaxation times in these patients' in liver MRI T2* was 5.44±6.7 msec.
- The mean ± SD relaxation time in these patients in heart MRI T2* was 28.34±19.5 msec.

The relaxation time of liver MRI was respectively ≥ 6.3 msec in 8(20%) patients, 6.3-2.7 msec in 16 (40%) patients and 2.7-1.4 msec in 11(27%)msec and less than 1.4 in 5(13%) patients(figure 1).

The relaxation time of cardiac MRI was respectively ≥ 20 msec in 26 (65 %) patients, 12-20 msec in 6 (15%) patients, 8-12 msec in 4(10%) patients and less than 8 msec in 4(10%) patients(figure 2).

Table 1: Relaxation times showing the severity of liver iron overload

Hepatic loading	Hepatic T2* (ms)
Normal	>6.3
Mild	6.3-2.7
Moderate	2.7-1.4
Severe	<1.4

Table 2: Relaxation times showing the severity of heart iron overload

Myocardial loading	Myocardial T2* (ms)
Normal	>20
Mild	12-20
Moderate	12-8
Severe	<8

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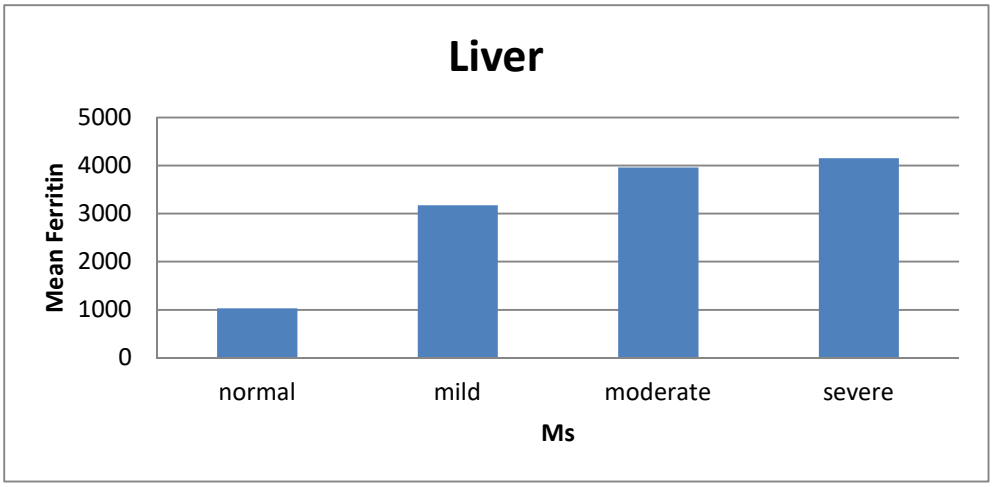
Figure 3: Relationship between Mean Serum levels of ferritin and hepatic T2*MRI



This graph shows there is moderate linear relationship between mean serum ferritin and condition of liver in terms of iron deposition , since with increase in mean serum ferritin level there is increasing haemosedirosis. Initially there is significant relation seen between mean serum ferritin and normal, mild and moderate iron overload but no such significant increase is observed in severe hepatic iron overload.

Figure 4: Relationship between Mean Serum levels of ferritin and cardiac T2*MRI

On the contrary in figure 4, there is no significant relation observed between increasing mean serum ferritin and cardiac iron overloading in MRI of patients with thalassemia major.

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Figure 5: Comparisons between hepatic and cardiac T2* MRI

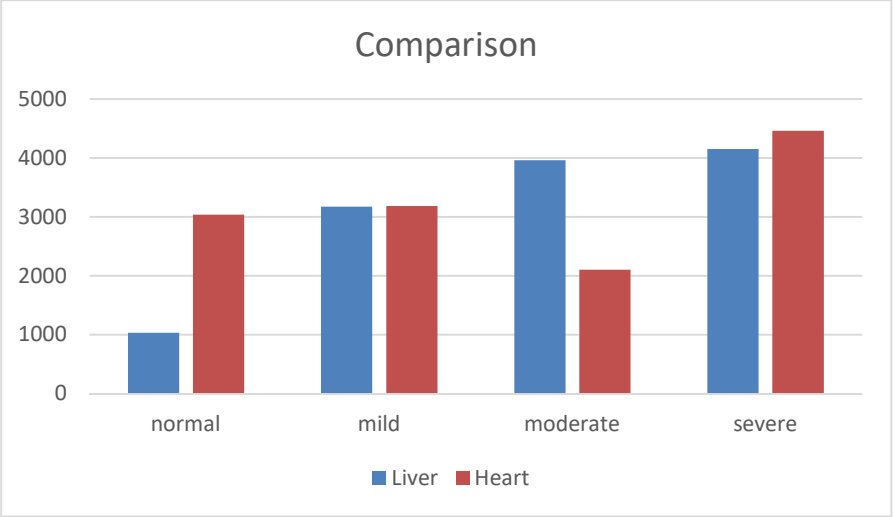
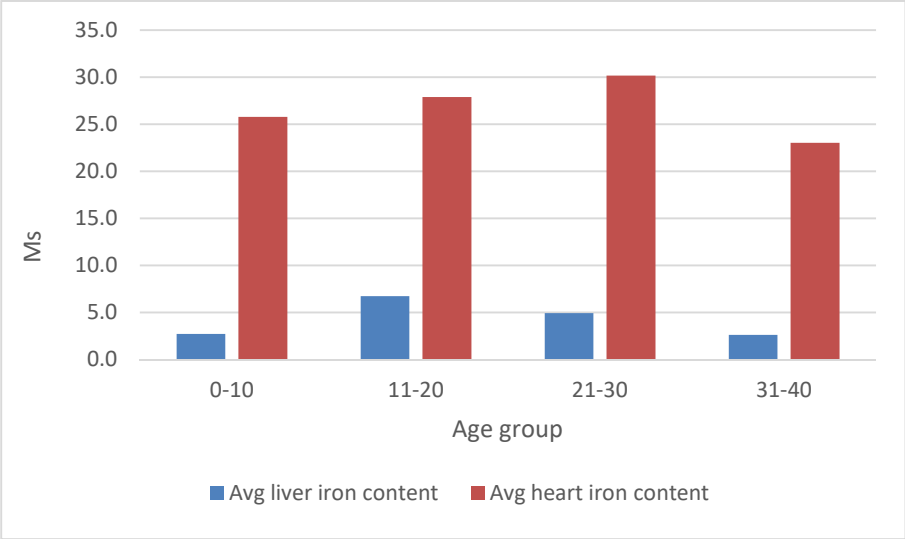


Figure 6: Relationship between age and average liver and heart iron content.



In figure 6 the x-axis represents the age groups and y-axis marks the relaxation time (Ms). Further we see that, even though heart iron content goes up with age till 30 years it does not correspond to this trend afterwards. Similarly there is no link between age and average liver iron content. Also the highest liver iron content is in the age group 11 – 20 yrs. Therefore, there is no correlation between age of the person and average iron content in both heart and liver.

DISCUSSION

In this study we focused our attention on whether the serum ferritin level could be considered a realistic parameter for the detection of iron overload in a population of thalassemic patients, most of whom were over 10 years old. Table 1 shows risk classification and the results of the MRI of liver and heart and mean ferritin levels of the 40 patients studied. In a study by Bandyopadhyay *et al*., patients even in the younger age group showed high serum ferritin levels. They found that in 1-5 years age group, average serum ferritin was 1750 ng/ml, and this increased to 3650 ng/ml in 11-15 years older patients. The serum ferritin level could not be controlled well as only few patients fully complied with recommended regimen at home. Similarly, in our study, the mean serum ferritin level was 3109.12±2386.94 ng/mL, which is markedly higher than the normal recommended

levels for normal individuals. Normal values of serum ferritin for men and women are 12-300 ng/mL and 12-150 ng/mL, respectively.

The values in our study are higher compared with similar regional and international studies. Cunningham *et al* in 2004 reported mean serum ferritin levels in beta thalassemia patients of North America to be 1696 ng/ml. However, Choudhry VP *et al* in India reported mean serum ferritin levels to be 6723 ng/ml even higher than in our study.

According to the relaxation time of liver MRI (table 2) we classified 8(20%) patients with no iron overload, 16 (40%) patients mild, 11(27%) patients with moderate and 5(13%) patients with severe iron overload(figure 1).Also, based on relaxation time of cardiac MRI (table 3) we classified 26 (65 %) patients with no iron overload, 6 (15%) patients with mild, 4(10%) patients with moderate and 4(10%) patients with severe iron overload(figure 2).

Figure 4 is showing correlation between mean serrum ferritin and MRI of liver, whereas figure 5 shows correlation between mean serrum ferritin and MRI of heart.

A significant correlation was observed between mean serum ferritin and liver iron content and no significant correlation was seen between mean serum ferritin and cardiac iron content. (Figure 5). Our results indicate a moderate negative correlation between liver MRI T2* relaxation times and serum ferritin. Therefore, it could be inferred that a higher level of serum ferritin is indicative of a higher liver iron level and vice versa. This is in line with study reported by Taghizadeh Sarvestani *et al* who showed ,a negative significant correlation was found between serum ferritin levels and liver MRI T2* ($P<0.05$, $r= -0.374$). However, no statistically significant association was observed between serum ferritin levels and heart MRI T2*($P>0.05$). Also, Azarkeivan *et al* demonstrated moderate negative correlation between serum ferritin and liver MRI T2* relaxation time ($r = – 0.535$) and a weak negative correlation between serum ferritin and heart MRI T2* relaxation time ($r = – 0.361$). Other studies have shown a significant correlation between ferritin level and the reported iron level of liver MRI T2* (13-15).

Moreover, the result showed that younger patients had higher levels of hepatic T2*MRI (figure 6). Therefore, there is no correlation between age of the person and average iron content in both heart and liver. Shamsian's study showed that there was a direct association between cardiac T2*MRI and mean of age. However, two similar studies proved a reverse association between T2*MRI and mean of age. Surekha Tony *et al* could not show a significant association between cardiac T2*MRI and serum ferritin.

We emphasize that our study presents data similar to those already reported concerning both comparisons between serum ferritin levels and direct measurement of hepatic iron. However, there are few data regarding thalassemia with a comparative analysis of several methods for measuring hepatic iron load. Nevertheless, we must conclude that ferritinemia is not always correlated with the true iron load status in thalassemic patients. In concert with these observations, Alberto *et al* demonstrated that measurement of serum ferritin did not have a prognostic value .The probable explanation for this observation may be obvious but further studies, which are in progress, are needed to demonstrate this conclusion.

Adequate assessment of iron burden cannot be determined by a single test. Liver MRI needs to be performed periodically, for example, once a year, and at shorter intervals for intensively chelated patients. SF must be measured at least 3 times a year. Measurement of liver iron allows real quantification of iron accumulation, the effectiveness of chelation and enables changes in strategy at a glance. This requires much time with SF. There

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are many other factors that influence iron loading and organ disease in thalassemia and treatment must be individualized. Perhaps the best strategy would be to use both techniques, mean SF and by MRI, frequently. Serial measurements of quantitative total liver iron may the best predictor of risk of organ injury. Further longitudinal studies in larger populations are needed to define risk.

CONCLUSION

Herewith we concluded , no correlation was seen between ferritin and cardiac iron storage, hence accurate assessment of cardiac iron load using MRI T2* is necessary in patients with β-thalassemia major. However, ferritin serum level is reliable to evaluate the liver iron level. Since these tests are more accessible and less expensive, they can be used for following patients to prevent further liver damage caused by iron overload.

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