

Original Research Article

A study of serum ferritin, alanine transaminase and hepatic MRI T2* values in β -thalassemia major patients

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ABSTRACT

Background: Present transfusion protocols have increased life expectancy of patients with β -thalassemia. Non-invasive T2* MRI is a newer technique in developing countries with promising role in management of thalassemia. Our goal was to assess the hepatic dysfunction in multi-transfused thalassemia patients by estimating iron overload using hepatic MRI T2* values, and correlating the results with serum ferritin and serum alanine transaminase (ALT) values.

Methods: This was a cross-sectional study of regularly transfused thalassaemia major patients from Thalassemia Center of Chacha Nehru Bal Chikitsalaya, M. Y. Hospital, a referral thalassaemia centre in Indore, Madhya Pradesh, India. The study was approved by the ethics committee of MGM Medical College, Indore, India. The study was conducted between August 2011 and September 2012. β -thalassaemia major patients who were regularly transfused and between the age of 5 to 15 years, were included.

Results: It was found that thirty three percent of the patients had hepatic MRI T2* values less than 6.3ms. Serum ALT levels were found to be above three times the normal range in 88% of patients. Significant liver iron deposition starts occurring at an early age leading to liver dysfunction. Serum ferritin levels did not linearly correlate with liver iron load thus it may not be a reliable marker for monitoring of chelation therapy.

Conclusions: For better management of thalassaemia patients, hepatic MRI T2* is suggested, instead of relying solely on serum ferritin.

Keywords: β -thalassemia major, Hepatic MRI T2*

INTRODUCTION

Thalassemia is an inherited hematologic disorder caused by a decrease or an absence of globin production.¹ β -thalassemia major refer to patient who requires early transfusion therapy and often is homozygous for β^0 mutations.² Present transfusion protocols have increased life expectancy of patients with β -thalassemia but they develop severe cardiopulmonary, liver, endocrine, and other major organ dysfunctions due to iron overload.³

Monitoring of iron overload closely and assessing it as accurately as possible is essential in establishing effective

iron chelation regimes, tailored to the individual patient's specific needs.⁴ Serum ferritin has been used as a marker for iron load in body, but it is not specific because its level can be raised in inflammations such as hepatitis, infections and in liver damage.⁵ Liver iron content serves as an indirect marker of total body iron.⁶ The liver contains about 70% of total body iron and is the main iron storage site in the body.^{7,8} Liver biopsy is the most reliable method for estimating organ iron overload but its invasive nature makes its implementation very limited, and its accuracy is greatly affected by hepatic inflammation, fibrosis and uneven iron distribution.⁵ Non-invasive T2* magnetic resonance imaging (MRI)

technique combines accurate, reproducible and platform-robust estimates of organ iron concentration with structural and functional correlations in patients with iron overload.⁹ Thus it has important implications for clinical management of iron overload and the tailoring of chelation regimes thereby reducing morbidity and mortality in thalassemia patients.

The present study evaluates serum ferritin level, ALT and hepatic MRI T2* values in β -thalassemia major patients.

METHODS

A cross-sectional study of regularly transfused thalassaemia major patients from Thalassemia Center of Chacha Nehru Bal Chikitsalaya, M. Y. Hospital, a referral thalassaemia centre in Indore, Madhya Pradesh, India was done. The study was approved by the ethics committee of MGM Medical College, Indore, India. The study was conducted between August 2011 and September 2012. β -thalassaemia major patients who were regularly transfused and between the age of 5 to 15 years, were included. Patients who were HBsAg positive, anti HCV antibody positive, or patients with cardiac anomaly, clinical heart failure were excluded from the study. All patients were under chelation therapy with oral iron chelators.

Written informed consent was taken from the parents of all participants and patients above 7 years had given assent. Alanine aminotransferase, serum ferritin levels and MRI T2* values were taken on routine monitoring of patients.

Liver function tests and serum ferritin measurements

ALT was estimated by IFCC (International Federation of Clinical Chemistry) method. Serum ferritin was estimated by chemiluminiscence method.

MRI quantification of hepatic iron

All subjects underwent MRI with a 1.5-T clinical system (Sonata, Siemens Healthcare) for routine liver protocol. R2* was calculated as the slope of the monoexponential fit of the natural log of signal intensity versus TE. The reciprocal of R2* is T2* ($T2^* = 1/R2^*$).

The observers placed four regions of interest (ROIs) in the liver parenchyma to measure the signal intensity in the right anterior, right posterior, left medial, and left lateral hepatic segments of each slice. ROIs measured approximately 2–3cm². Mean and SD T2* values for all four ROIs in each patient were recorded, and values were averaged.

Liver MRI T2* values <1.4ms were considered as severe iron load. 1.4 to 2.7ms was moderate while 2.8 to 6.3ms was mild iron load. Values >6.3ms was considered as normal. Liver MRI T2*, ALT, serum ferritin level,

hepatitis C antibody, HBsAg was done in all patients and were conducted within a 2-month period for all patients.

RESULTS

Of the 18 β thalassemia major patients, 8 patients belong to age group 5-10 yrs, and 10 patients belong to age group 11-15 yrs. Female were 10 while 8 were male. The mean blood transfusion requirement was 157 mL/kg/year with a range of 120-185 mL/kg/year. Serum ferritin was found to range from 1824 to 7650ng/ml with a mean value of 4930 ng/ml. None of the patients had undergone splenectomy. All patients were on oral iron chelators.

Table 1: Patients' demographic and clinical characteristics.

Variable	Value
Number of cases	18
Sex(M/F)	8/10
Age	
Range	6-14 years
Mean	9.85 years
Annual blood requirement(ml/kg/year)	
Range	120-185
Mean	157
Splenectomy	None
Aspartate aminotransferase (U/L)	
Mean	173
Range	56-287
Ferritin (ng/mL)	
Mean	4930
Range	1824-7650
Liver MRI T2* (ms)	
Range	1.5-29.4

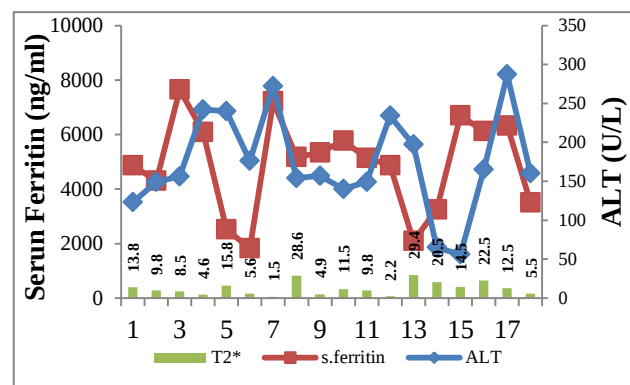


Figure 1: Correlation between serum ferritin levels, hepatic MRI T2* and ALT level.

Liver MRI T2* values was found to be in range of 1.5 to 29.4ms. Thirty three percent of the patients had mild to moderate iron overload. Serum ALT levels were found to be above three times the normal range in 88% of (16 out of 18) patients.

Demographic profile, medical characteristics and clinical findings of the patients with thalassemia are shown in Table 1.

The correlation between serum ferritin levels, hepatic MRI T2* and ALT is shown in Figure 1. Due to small number of patients, statistical analysis could not be validated. It is observed that a negative correlation exists between liver MRI T2* relaxation time and serum ferritin, but it doesn't hold true for all the cases. Discrepancy is seen in some cases where serum ferritin doesn't truly represent body iron load. Alanine aminotransferase (ALT) was found to be above normal in all the cases. It was higher in cases with low hepatic T2* values.

DISCUSSION

Regular transfusion in thalassemia major patients causes iron overload because human body lacks a mechanism to excrete excess iron. Monitoring of iron overload is essential in establishing effective iron chelation regimen. In the present study, one third of the patients had hepatic MRI T2* values less than 6.3 ms. In a similar study by Xuedong WU, hundred percent patients had hepatic T2* values less than 6.3 ms as children more than 10 years of age were included in the study.¹⁰ Another study by Eghbali A et al reported 77 percent of the patients with hepatic T2* values less than 6.3ms, with mean age of patients to be around 17 years.¹¹ Present study is corresponding with previous studies and suggests an early significant hepatic iron deposition in patients with thalassemia.

Various studies suggested a moderate negative correlation between liver MRI T2* relaxation times and serum ferritin.^{12,13} The results indicate that serum ferritin and liver MRI T2* can be negatively correlated but it doesn't hold true for all the cases. The study is in concordance with other studies, which concluded that prediction of iron loading from serum ferritin can be unreliable.¹⁴ They also reported that a simple relationship between serum ferritin and iron stores cannot be assumed when ferritin concentrations are high.¹⁵

In present study, serum ALT levels were found to be above three times the normal range in 88% of patients. This is consistent with other studies. Sengsuk et al found liver functions to be 3-4 folds higher in β -thalassemia patients. Iron overload associated with increased oxidative stress, lipid peroxidation and liver damage is causative in transfusion dependent β -thalassemia major.¹⁶ Jensen et al also observed that serum transaminases and hepatic fibrosis progresses with increase in hepatic iron concentration.^{17,18} In the study, it was found that liver dysfunction starts at an early age even in the absence of HBV and HCV infections in thalassemia major patients. The main limitation of present study was lesser number of patients.

CONCLUSION

Significant liver iron deposition starts occurring at an early age leading to liver dysfunction. Serum ferritin levels did not linearly correlate with liver iron load thus it may not be a reliable marker for monitoring of chelation therapy. Thus liver iron quantification may be a better tool for it. MRI is better tool as it is non-invasive and eliminates complications of biopsy. To better evaluate the haemosiderosis status among thalassaemia patients, a routine evaluation of liver iron content using MRI T2* is suggested, if possible, instead of relying solely on serum ferritin. These interventions will prevent liver damage so that morbidity and mortality can be prevented along with better quality of life in thalassemia major patients.

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