RESEARCH PAPER

Evaluation of Cardiac Iron Load by Cardiac Magnetic Resonance in Thalassemia

RASHID MERCHANT, ADITI JOSHI, JAVED AHMED, *PRADEEP KRISHNAN AND *BHAVIN JANKHARIA

*From the Department of Pediatrics, Dr Balabhai Nanavati Hospital, Mumbai, India; and *Piramal Diagnostics, Mumbai, India.*

Correspondence to: Dr Rashid H Merchant, 501, Rangmahal 5th floor, 2 Mount Mary Road, Bandra (West), Mumbai 400 050, India. deandoc2000@hotmail.com

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Objective: To quantify myocardial iron stores by Cardiac Magnetic Resonance (CMR) .

Design: Prospective cohort study.

Setting: Thalassemia center in a teaching hospital.

Participants: 60 transfusion dependant thalassemia major patients and 10 controls during 2008-2009.

Methods: MRI T2* for cardiac iron load and cardiac functions was performed on a 1.5 Tesla Siemens Sonata machine using the thalassemia tools software. Ejection fraction (EF) was measured using standard CMR sequence and EF <56% considered as cardiac dysfunction. Quantification of iron deposition was categorized as T2* <10 milliseconds (ms) as high risk, 10-20 ms as intermediate risk and >20 ms as low risk. Simultaneous liver iron T2* values were categorized into normal i.e. >6.3 ms, mild iron overload 6.3 - 2.7 ms , moderate iron overload 2.7- 1.4 ms and severe iron overload <1.4 ms. Pretransfusion serum ferritin levels were simultaneously determined. Data was analyzed by paired and unpaired *t* test of mean.

Results: Of 60 patients, 50% had no cardiac siderosis; 33.3% had mild to moderate and while 16.7% had severe cardiac siderosis . In contrast, only 8.3% had normal liver iron values, 55.7% had mild to moderate and 36% had severe iron stores. The mean serum ferritin of all 60 cases was 3528.6 ± 1958.6 ng/mL. There was a statistically significant difference in the mean cardiac T2* of patients (23.45 ± 13.4 ms) as compared to controls (32.67 ± 2.68 ms) (*P*<0.01).

Conclusions: Thalassemia patients had significantly higher cardiac iron stores as compared to controls. Serum ferritin and liver iron values did not correlate with cardiac iron values. Three of 10 patients <10 years showed evidence of myocardial siderosis.

Key words: *Cardiac siderosis, Magnetic resonance imaging, Myocardial dysfunction, Thalassemia*

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Despite the availability of iron chelation, cardiac iron overload accounts for most deaths in thalassemia major. Without adequate iron chelation myocardial siderosis develops within the first decade of life and leads to progressive cardiomyopathy. Measurement of cardiac iron presents a major challenge as neither serum ferritin nor liver iron, are reliable indicators of cardiac iron overload. Cardiovascular magnetic resonance (CMR) is the established gold standard for quantifying cardiac iron and ventricular function [1].

Measurement of cardiac iron by T2* on MRI provides useful information on severity of myocardial siderosis [1]. T2* gradient echo measures decay in signal intensity as echo time of images progressively increases. This rate of decay is enhanced in presence of iron deposition and hence

increased iron levels reduce T2* values. Cardiac T2* value <20 milliseconds (ms) is indicative of iron overload and below this value there is progressive decline in left ventricular function. Values of <10 ms are considered suggestive of severe cardiac siderosis. Thus, T2* can be used as a guide to severity of cardiac risk i.e. >20ms as low, between 20-10 ms as intermediate and <10 ms as high risk [2].

The aim of this study was to assess cardiac iron overload and evaluate cardiac function using a single slice multi echo T2* MR sequence and cine imaging in patients with thalassemia major.

METHODS

60 regularly transfused thalassemia major patients (34 males) ages ranging from 6 to 26 years (mean 17 years) and 10 healthy, age - matched controls were studied. All patients were on regular blood transfusion administered at 2-4 weekly intervals to maintain the pretransfusion hemoglobin of at least 8 g/dL. Informed consent was obtained from patients or guardians and the hospital ethical committee approved the study protocol. Of 60 cases, 41 were receiving oral deferiprone (L1) at 60-65mg/kg/day, 16 receiving combination of L1 (60-65mg/kg) along with desferrioxamine (DFO) subcutaneously (30-35mg/kg) for 5 days a week, while 3 were receiving only DFO. All cases tolerated chelation therapy well.

T2* for cardiac iron was performed using 1.5 Tesla Siemens Sonata machine and all patients were scanned using a single 8 mm thick, short-axis, mid-left ventricle slice acquired at 8 different echo times. Systolic and diastolic ventricular volumes and EF were measured using a standard, reproducible CMR sequence and a semi-automated software, as per published norms [3,4]. EF of <56% was considered to represent cardiac dysfunction. Serum ferritin levels were estimated by ELISA from a pretrans-fusion sample. Although hepatic iron stores were simultaneously measured using a similar technique to the heart with a non-ECG gated multi-echo sequence, it did not form part of the primary study analysis.

Data are presented as mean ± standard deviation (SD). Variables were analyzed by paired and unpaired t test of means to determine statistical differences and *P* value <0.05 was considered statistically significant for any given measure.

No attempt was made in this study to analyze the effects of iron chelation on extent of cardiac iron overload.

RESULTS

Patient demographics, ventricular parameters, cardiac T2* and liver T2* values are shown in ***Table* I**. The mean blood transfusion requirement was 219.42 ml/kg/year with a range of 180-266 mL/kg/year. The mean serum ferritin of all 60 cases was 3528.6 ± 1958.6 ng/mL.

Cardiac T2* values in relation to serum ferritin and liver T2* are depicted in ***Fig.* 1** and **2,** respectively. Of 60 subjects, 50% had normal cardiac iron load (>20 ms), 33.3% had mild to moderate cardiac siderosis (20-10 ms) and 16.7% had severe cardiac siderosis (<10 ms). In contrast, only 8.3% subjects had a normal liver iron (>6.3 ms), 55.7% had mild to moderate liver iron load (6.3-1.4 ms) and 36% had severe liver iron load (<1.4 ms). Moderate to severe liver iron involvement was noted in 81% of patients. Abnormal cardiac T2* (<20 ms) was found in 33.3%, 54.3% and 37.5% in the age group of <10 ,

TABLE I DEMOGRAPHICS, HEMODYNAMICS, CARDIAC AND LIVER MRI T2* RESULTS (*N*=60)

Parameter	Range	Mean
Age (y)	6-26	17
Serum Ferritin ng/mL	133-7500	3528.6 ± 1958.6
Cardiac T2* ms	6.24-69.9	23.45 ± 13.4
<10 y (*n*=10)	12.68-50.62	25.82
10-20 y (*n*=33)	6.24-69.19	22.32
>20 y (*n*=17)	8.22-44.84	24.26
LVEF (%)	50.9-76.2	62.87
EDV (mL)	37.9-148.7	86.1
ESV (mL)	10.9-69.9	32.56
Liver T2* ms	0.93-16.2	2.7
<10 y (*n*=10)	1.07-5.09	1.92
10-20 y (*n*=33)	0.93-12.65	2.46
>20 y (*n*=17)	1.09-16.2	3.71

LVEF- left ventricular ejection fraction; EDV-end diastolic volume, ESV-end systolic volume; ms – milliseconds.

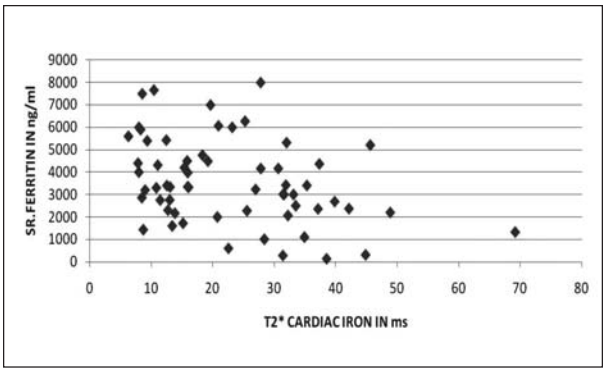

FIG. 1 *Relation between serum ferritin and cardiac T2*.*

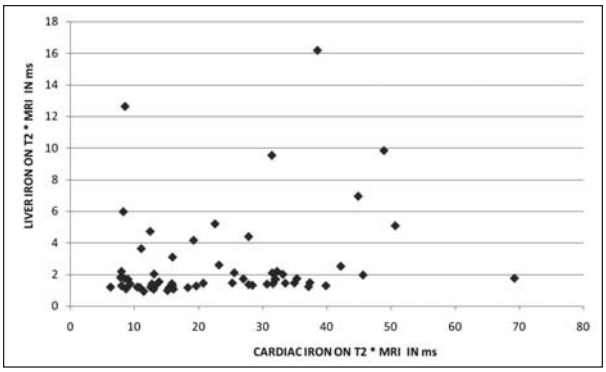

FIG. 2 *Relationship between liver and cardiac T2*.*

10-20 and >20 years, respectively. There was a statistically significant difference ($P<0.01$) in the mean cardiac T2* value of the 60 patients (23.45 ± 13.4ms) as compared to that of 10 controls (32.67 ± 2.68 ms). Liver iron correlated poorly with myocardial iron concentration (***Fig.* 3**). In the present study, there was no difference in the SF or liver iron T2* levels between those with or without detectable cardiac siderosis.

DISCUSSION

In thalassemia, iron overload occurs as a result of repeated blood transfusions and excessive iron absorption from the gut [1,3]. The human body has no mechanism of excreting excess iron, which gets deposited into body tissues, including cardiomyocytes, leading to iron induced cardiac disease. When the iron binding capacity of transferrin is saturated, free iron appears as non transferrin bound iron. This toxic labile cellular iron causes generation of oxygen free radicals resulting in oxidative stress, leading to impaired function of the mitochondrial respiratory chain of the myocardium and to cardiac dysfunction [1,3]. As iron accumulates in the myocardium, there is little effect on its contractile function until a critical threshold is reached above which rapid deterioration can occur. This explains why abnormal systolic function is a late sign of cardiac toxicity in thalassemia. Severe myocardial siderosis causes a toxic dilated cardiomyopathy that can be reversed if aggressive chelation is begun early [5]. Recently, non-invasive assessment of myocardial iron with magnetic resonance relaxometry has been evaluated [1].

Iron deposits cause magnetic field inhomogeneity and shorten the relaxation parameters T1, T2 and T2*. Prior to the introduction of cardiac T2* quantification there was no accurate measure to predict risk of iron induced cardiac disease in TM and the risk of developing heart failure was estimated by sequential SF or liver iron concentration. Evidence is also available from animal studies [6] that cardiac iron load correlates well with cardiac T2*, and work is underway to provide a calibration of T2* for myocardial iron load in human [7]. Measurement of T2* is now widely used for the heart as it is easily combined with cardiac gating, is fast and robust, and is sensitive to iron deposition [4].

In the present study, we have shown that 50% of the patients had significant cardiac iron overload (T2* <20ms). The prevalence of severe cardiac iron overload (T2*<10 ms) in our study population was 16.7%. Even in patients under the age of 10 years, a high degree of iron loading was found with 33.3% having a myocardial T2* <20ms. There were 10 patients under 10 years. Three of these had T2* <20 ms, the youngest one being a 6 year old with T2* value of 12.7ms, suggesting very early onset of cardiac siderosis.

Liver iron overload was found in 93% of the patients with 53% having evidence of severe hepatic siderosis (T2*<1.4 ms). Despite this, only 2 patients (3.3%) had evidence of impaired LV systolic function (EF <56%). There was no difference in the SF or liver T2* levels between those with or without detectable cardiac siderosis. To confirm that these

WHAT IS ALREADY KNOWN?

- Gradient echo T2* MR provides a rapid, noninvasive, reproducible means for assessing myocardial iron.

WHAT THIS STUDY ADDS?

- Thalassemia patients had significantly higher cardiac iron stores as compared to controls, and cardias siderosis was found at an early age in poorly chelated patients.

findings were not spurious, the mean SF values for 12 months prior to the scan were compared to cardiac T2* and there was no significant correlation. The mean value for cardiac T2* in the normal healthy controls was 32.67 ± 2.68ms and there was a significant difference in mean cardiac T2* values (P<0.01) between controls and the study population.

As expected, there was a significant difference in mean cardiac T2* values between controls and study population. These findings compare well with previous data in Caucasians [1]. Normal ranges for T2* have been determined from observational data in normal population and patients with thalassaemia. The threshold of T2* <20 ms as an index of cardiac risk is widely accepted with increasing risk of heart failure and arrhythmias when T2* is below 10ms [8]. It is important to note that these ranges are only applicable at a field strength of 1.5 Tesla.

In our study population, the age, transfusion requirements, and compliance to chelation therapy were so tightly connected that it was not possible to decipher which of these individual factors was mainly responsible for cardiac siderosis. While T2* gives an accurate impression of cardiac iron, it is not yet possible to predict the exact myocardial iron concentration from the T2* values we determined. A full calibration would require correlation with myocardial tissue. Although myocardial tissue can be obtained from myocardial biopsy, this is a difficult, invasive procedure with risk of life threatening complications. There is also the issue of non homogenous myocardial iron deposition and therefore biopsy is not clinically useful as an index of cardiac iron load [8-12].

The majority of our patients with significant cardiac siderosis would have been considered at low risk for cardiac disease on the basis of serum ferritin level alone. We have confirmed that liver iron correlates poorly with myocardial iron concentration and in agreement with observational data from other studies, we found no difference in the SF or liver iron T2* levels between those with or without detectable cardiac siderosis [1,13]. The unreliable predictive value of SF measurements has made heart disease difficult to detect and cardiac failure and arrhythmias remain the leading cause of death [5,14]. SF is not a sensitive predictor of subclinical cardiac disease and cardiac deaths can occur even with SF levels <2500 ng/mL [9]. Once cardiac decompensation occurs, there is a high risk of death unless chelation therapy is dramatically intensified [14-19]. Values <10 ms indicate high levels of cardiac iron and high risk of cardiac decompensation [8]. It is recommended that MRI T2* should be repeated every 2 years if T2* >20ms, every year if between 20-10 ms, every 6 months if <10 ms and even earlier if evidence of cardiac dysfunction is documented. In a population who have not received any form of iron chelation, this evaluation may be necessary even in younger patients [20,21].

This was a heterogeneous population with different chelation regimes and with problems in compliance with chelation, hence we cannot extrapolate these results to all thalassemic patients in India. Moreover, the study had a small sample size in which iron overload was not compared with different chelation regimes.

In conclusion, we have demonstrated that cardiac siderosis is present in a high proportion of patients and that this can occur at a very early age (even below 10 years). In spite of significant cardiac iron deposition, cardiac function in this cohort was relatively well maintained. Serum ferritin and liver iron did not correlate with the severity of cardiac iron overload. These findings have important impli-

cations for the monitoring and routine management of thalassemia patients.

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