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Low Prevalence of Cardiac Siderosis in Heavily Iron Loaded Egyptian Thalassemia Major Patients

AMAL EL BESHLAWY, M.D.[1]; MONA EL TAGUI, M.D.[1]; MONA HAMDY, M.D.[1]; MONA EL GHAMRAWY, M.D.[1]; KHALED ABDEL AZIM, M.D.[1]; DORIA SALEM, M.D.[2]; FADWA SAID, M.D.[3]; AHMED SAMIR, M.D.[4]; TIMOTHY St PIERRE, M.D.[5] and DUDLEY J. PENNELL, M.D.[6]

The Departments of Pediatrics[1], Cairo University, Radiology[2], Clinical Pathology[3], Cairo University, Radiology[4], Ain Shams University, Cairo, Egypt, School of Physics[5], University of Western Australia, Perth, Australia and Royal Brompton Hospital[6], London, United Kingdom

ABSTRACT

Background: Myocardial siderosis in thalassemia major remains the leading cause of death in developing countries. Once heart failure develops, the outlook is usually poor with precipitous deterioration and death. Cardiovascular magnetic resonance (CMR) technology can measure cardiac iron deposition directly using the magnetic relaxation time T2*. This allows earlier diagnosis and treatment and helps to reduce mortality from this cardiac affection.

Aims: To find out the prevalence of cardiac siderosis among our patients who are heavily iron loaded by CMR technology and its relation to liver iron concentration, serum ferritin and left ventricular ejection fraction.

Patients and Methods: Eighty nine ß-thalassemia patients (10 to 43 years, mean age of 20.78±6.36) were recruited in this study. All patients were receiving chelation therapy of subcutaneous desferroxamine. Evaluation of hemosiderosis was based on CMR, liver magnetic resonance R2 and serum ferritin.

Results: Cardiac T2* values ranged between 4.3 to 53.8 ms with a mean of 28.5±11.7ms. The left ventricular ejection fraction (LVEF) as measured by CMR ranged between 55 and 78% with a mean of 67.7±4.7% and liver iron concentration (LIC) ranged between 1.5 to 56mg/g dry weight with a mean of 26.1±13.4mg/g. Serum ferritin varied from 533 to 22360ng/ml; mean=4510±2847ng/ml with 83.2% above 2500ng/ml. The prevalence of myocardial siderosis (T2*<20ms) among our patients was 22/89 patients (24.7%) whose mean age was 20.9±7.5 years with a mean T2* value of 12.7±4.4ms and LVEF of 68.6±5.8%, LIC and serum ferritin level of 30.9±13.5mg/g and 6120±4190ng/ml respectively. There was no correlation between T2* results and the age, LVEF, LIC and serum ferritin of this group (p=0.65, p=0.085, p=0.99 and p=0.63 respectively). Patients with severe cardiac siderosis (T2*<10ms) constituted 7/89 (7.9%) with a mean age of 18.4±4.4 years. Although these patients had a mean T2* of 7.8±1.7ms, the LVEF value was 65.1±6.2% and only one patient had clinical cardiac disease (T2*=4.3 ms and LVEF=55%). LIC and serum ferritin levels were 29.8± 17.0mg/g and 7200±6950ng/ml respectively. In this group of severe cardiac siderosis, T2* was not correlated to age (p=0.5), LVEF (p=0.14), LIC (p=0.97) or serum ferritin (p=0.82).

Conclusion: There is a low prevalence of myocardial siderosis in the Egyptian thalassemia patients in spite of very high serum ferritin. Cardiac T2* is the best test that can identify at risk patients who can be treated with optimization of their chelation protocols. The possibility of a genetic component for the resistance to cardiac iron loading in our population should be considered.

Key Words: *Cardiac siderosis – Thalassemia major.*

INTRODUCTION

Myocardial siderosis remains the leading cause of death in thalassemia major in developing countries. Once heart failure develops, the outlook is often poor with precipitous deterioration and death **[1,2]**.

Methods for predicting heart failure have been developed that are based on established measures of iron loading, most importantly, serum ferritin >2500µg/L **[2]** and liver iron concentration >15mg/g dry weight **[3]**. However, the persistently high mortality rate from heart failure indicates that high risk patients are not being identified in time for effective intervention.

Measurement of ventricular function such as alteration over time in ejection fraction has also been proposed in thalassemia, but it identifies patients at relatively late stage **[4]** and dysfunction may be masked because of supranormal left ventricular function in thalassemia

patients in absence of myocardial iron loading **[5]**.

Most recently, assessment of myocardial iron with magnetic resonance (CMR) relaxation time T2* has been used. The measurement of T2* is fast, robust and the most sensitive to iron deposition **[6]**. The classification of patients is that those with T2*>20ms are regarded as not having cardiac iron, those with T2* between 10-20ms have mild to moderate cardiac iron load and those <10ms are considered to have heavy cardiac iron load **[7]**.

Our objectives were to find out the prevalence of cardiac siderosis among our patients using T2* CMR and relate the findings to liver iron concentration, serum ferritin and left ventricular ejection fraction.

PATIENTS AND METHODS

Eighty nine multiply transfused ß–thalassemia major patients, following at the Hematology Clinic of the New Children's Hospital of Cairo University, were selected to participate in this study after the approval of the ethical committee and after signing a written informed consent. Their age ranged between 10 to 43 years; (mean age = 20.78±6.36 years).

All patients were receiving chelation therapy in the form of subcutaneous desferroxamine.

Patients were evaluated for:

Cardiac siderosis and left ventricular ejection fraction (LVEF) by cardiovascular magnetic resonance (CMR), using relaxation parameter T2* **[8]**: A single 10 mm thick short-axis mid-ventricular slice of left ventricle was acquired at 8 echo times with standard shimming in a single breath-hold. For analysis, a full thickness region of interest was chosen in the LV septum.

Liver iron concentration (LIC) measurements were conducted on a Philips Intera (Netherlands) 1.5-T MRI scanner. LIC measurements were made using SDPA R2-MRI (FerriScan®). Detailed methodology is described elsewhere **[9,10,11]**. Axial images were acquired with a multislice single spin-echo (SSE) pulse sequence, with a pulse repetition time TR of 2500ms, spin echo times TE of 6, 9, 12, 15, and 18ms, and slice thickness of 5mm. For each subject, the largest axial slice of the liver was selected for R2 image analysis and LIC calculation.

Serum ferritin was performed by microparticle enzyme immunoassay (Abott AXSYM System).

Statistical methods:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t*-test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. Correlation between various variables was done using Pearson moment correlation equation. *p*-values less than 0.05 was considered statistically significant.

RESULTS

T2* values of all patients ranged between 4.3 to 53.8ms with a mean of 28.5±11.7ms. The left ventricular ejection fraction (LVEF) as measured by CMR ranged between 55 and 78%; mean = 67.7±4.7%,.and liver iron concentration (LIC) ranged between 1.5 and 56mg/g dry weight with a mean of 26.1±13.4mg/g. Serum ferritin varied from 533 to 22360ng/ml; mean = 4510±2847ng/ml with 83.2% above 2500ng/ml (Fig. 1).

Myocardial siderosis (T2*<20ms) was encountered in 22/89 patients (24.7%) whose mean age was 20.9±7.5 years with a mean T2* value of 12.7±4.4ms and LVEF of 68.6±5.8%. LIC and serum ferritin levels were 30.9± 13.5mg/g and 6120±4190ng/ml respectively (Table 1).

There was no correlation between T2* results and age, LVEF, LIC or serum ferritin of this group (p=0.65, p=0.085, p=0.99 and p=0.63 respectively) (Figs. 2,3,4).

There were 7/89 patients (7.9%) with severe cardiac siderosis (T2*<10ms) with a mean age of 18.4±4.4 years. Although these patients had a mean T2* of 7.8±1.7ms, the LVEF value was 65.1±6.2% and only one patient had clinical cardiac disease (T2*=4.3 ms and LVEF=55%). LIC and serum ferritin values were 29.8± 17.0mg/g and 7200±6950ng/ml respectively. In this group of severe cardiac siderosis, T2* was not correlated to age (p=0.5), LVEF (p=0.14), LIC (p=0.97) or serum ferritin (p=0.82).

Table (1): ß-thalassemia major Patients with T2* >20ms versus patients with cardiac siderosis T2* <20ms.

	Patients T2* >20ms (n-67)		Patients T2* <20ms (n-22)	
	Mean	Std.D	Mean	Std.D
Age (yrs)	20.8	6.0	20.9	7.5
T2* (ms)	33.7	8.2	12.7	4.4
LVEF (%)	67.4	4.3	68.6	5.8
LIC (mg Fe/gdw)	24.6	13.1	30.9	13.5
Ferritin (ng/ml)	3986	2023	6120	4190

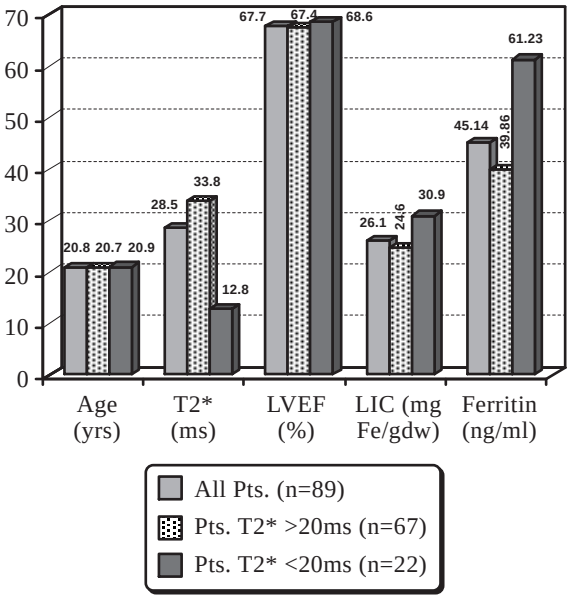

Fig. (1): Comparison of the mean age, T2*, LVEF, LIC and ferritin values in 89 thalassemia major patients and in relation to cardiovascular magnetic resonance (T2*).

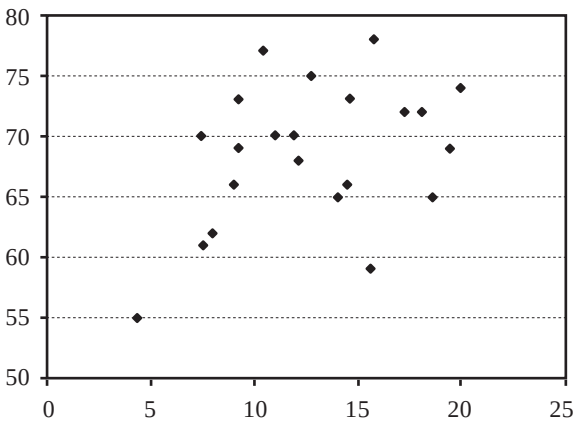

Fig. (2): Correlation between T2* and LVEF in 22 thalassemia major patients with cardiac siderosis (T2* <20ms).

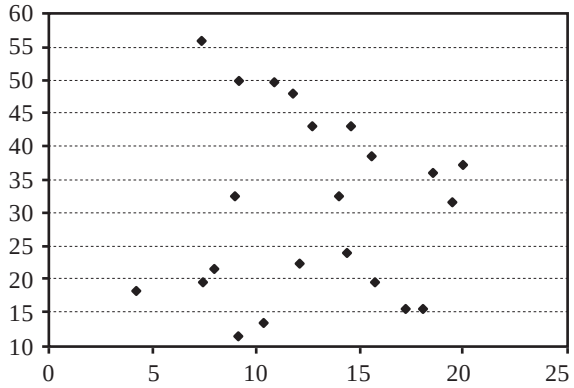

Fig. (3): Correlation between T2* and LIC in 22 thalassemia major patients with cardiac siderosis (T2* <20ms).

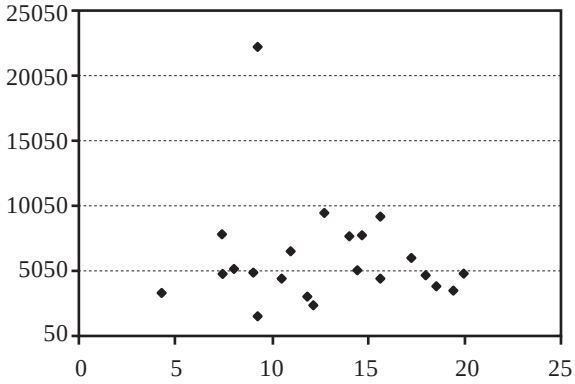

Fig. (4): Correlation between T2* and serum ferritin in 22 thalassemia major patients with cardiac siderosis (T2* <20ms).

DISCUSSION

Low values of liver iron or serum ferritin do not necessarily signify low risk of iron–induced cardiomyopathy **[6]**. Therefore, there is often a need to identify those thalassemia patients most at risk of cardiomyopathy even when serum ferritin and liver iron values are currently well controlled. Although sequential quantification of heart function identifies a patient group at increased risk of cardiac mortality, **[4]** it would be preferable to identify high-risk patients early before cardiomyopathy develops and use targeted treatment **[12,13]**. The estimation of heart iron by MR offers this possibility. We have used the MR relaxation parameter T2*, which is sensitive to the presence of storage iron microaggregates which disturb the homogeneity of the magnetic microenvironment.

The prevalence of myocardial siderosis (T2*<20ms) in this cohort study of Egyptian patients was 24.7%. These subjects were be-

lieved to have a broad range of compliance (ferritin 533-22360ng/ml, mean of 4510ng/ml) and as such are likely to be fairly representative of the thalassemia major population as a whole in Egypt. This rate was much lower than those previously reported by different studies around the world; 65%, 50%, 30%, 46%, 64%, 86% **[7,14-18]**.

There was no correlation between cardiac T2* and liver iron concentration among our studied group. It has been described in several prior studies **[6,7,15]** that on cross-sectional evaluation, there is marked disconnect between liver and heart iron values **[19]**. One reason for this disconnect is organ specific mechanisms of iron uptake/release. Liver, bone marrow and spleen are the natural reservoirs for iron and transferrin-bound iron is shuttled among these stores in a tightly regulated manner. The heart and endocrine glands also have well-regulated transferrin-mediated uptake, but pathologic iron deposition in these organs occurs through unregulated influx of non-transferrin-bound iron (NTBI) **[20,21]**. NTBI levels rise once transferrin is fully saturated and are modulated by the type and duration of chelator exposure **[22]**.

In addition to differences in iron uptake, there are differences in iron elimination as chelation therapy can remove iron more rapidly from the liver than from the heart, which may normalize liver iron while myocardial iron remains high **[6,23,19]**. Other mechanisms may be involved, including potential genetic variations in function of cardiac iron transport channels such as the L-type calcium channel and the divalent metal transporter 1 **[24,25]**. The discordance between liver and myocardial iron indicates that the risk of heart complications cannot be predicted solely from liver iron measurement **[7]**.

Myocardial T2* had no correlation with serum ferritin among our studied group. Cohort studies have failed to show any significant correlation between heart T2* and serum ferritin **[6,7,16,28]** or very weak relation **[26,27]**. The relation between serum ferritin and myocardial iron loading indicates that whilst a high ferritin may be bad, a low ferritin cannot be taken as reassuring **[7]** and total body iron stores have little immediate predictive value with respect to the presence or absence of cardiac iron **[28]**.

We observed no correlation between T2* and age of the patients, similar results were previously reported **[15,16]** denoting the possibility of a genetic component for the susceptibility of cardiac iron loading in some populations. However, Wood and colleagues showed that the relationship between T2* and age was fundamentally non-linear **[28]**.

There was a trend towards correlation between T2* and ejection fraction but this was not statistically significant (p=0.085). Positive correlation was observed in different studies **[6,15,17,29,30]**. There is significant variation in ejection fraction between patients with similar levels of iron loading. Thus a once-off ejection fraction measurement may be inadequate for assessing the cardiac risk resulting from myocardial siderosis **[7]**. The relationship between T2* and cardiac function is shallow until a critical level is reached, after which rapid deterioration occurs. This explains why identification of abnormal systolic function is a late sign of iron toxicity **[6]**. However, in the study of Daar and colleagues **[16]**, there was no correlation between ejection fraction and cardiac T2*. Ejection fraction in their group of patients was measured by routine echocardiography, which is a less accurate and reproducible technique than CMR **[31]**.

Among our patients, 7.9% had severe cardiac siderosis. Higher prevalence of severe cardiac siderosis was reported among different groups **[7,14,16,17]**. One patient had clinical heart failure (LVEF=55%) in contrary to previous reports of impaired ventricular function in 45%, 62% and 19% among severe cardiac siderosis **[7,14,17]**. Chirnomas and colleagues showed that systolic function has poor sensitivity for detecting elevated myocardial iron as 18% of their patients had elevated myocardial iron with a normal ejection fraction **[15]**. Left ventricular function falls with decreased myocardial T2*, and this is accompanied by left ventricular dilation and hypertrophy; all of which are classic cardiac responses of heart failure **[6,27]**.

What was of more concern was the fact that the other 6 patients in this group of severe cardiac siderosis were asymptomatic and had normal ejection fractions. These patients are at the highest risk of developing clinically significant myocardial complications such as cardiac

failure and life-threatening ventricular arrhythmias.

Conclusion:

There is a low prevalence of myocardial siderosis in the Egyptian thalassemia patients in spite of very high serum ferritin.

Cardiac T2* is the best test that can identify at risk patients who can be treated with optimization of their chelation protocols. The possibility of a genetic component for the resistance to cardiac iron loading in our population should be considered.

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