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ORGINAL ARTICLE

Evaluation of Myocardial Siderosis in Children with Beta Thalassemia at Hematology Unit of Zagazig University Hospital

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ABSTRACT

Background: T2-star (T2*) magnetic resonance imaging is sensitive and non-invasive tool to evaluate myocardial load of iron in beta thalassemia major patients. This study aimed to determine cardiac iron load in children with thalassemia major by using T2* MRI to allow an early management.

Methods: Cross sectional study was performed on 100 beta thalassemia patients (55 males, 45 females) in the period from May 2017 to April 2019. MRI heart and liver was done to detect myocardial and hepatic iron burden. Genotype was detected by DNA sequence technology.

Results: The mean cardiac T2* value was 28.2 ms and mean hepatic content of iron was 14.4 mg/g dw. β0β0 genotype was the most aggressive genotype as regard to myocardial iron overload development. Strong correlation was found between myocardial iron overload and each of hepatic iron burden and serum ferritin.

Conclusion: Myocardial iron overload was a critical problem in beta thalassemia major patients with a marked association with genotype, liver iron content and serum ferritin.

Key words: Myocardial iron overload, thalassemia, T2* MRI, genotype

INTRODUCTION

Thalassemia is considered one of the most common inherited hematological disorders all over the world **[1]**.

The leading cause of mortality in Thalassemia major patients is iron overload caused by frequent blood transfusion, which lead to damage to heart, liver and endocrine glands **[2]**. Myocardial siderosis causes cardiomyopathic changes on the heart which can be prevented if chelation agents are administrated early, but the delay in diagnosis is usually related to late occurrence of symptoms **[3]**. The most useful way to detect hepatic iron level is biopsy; but, it is invasive maneuver and can't measure iron in the heart accurately **[4]**.

Recently, non-invasive T2* MRI is a way for evaluation of iron complexes as ferritin induce T2 relaxation enrichment **[5]**. The aim of this work is to assess myocardial siderosis in patients with beta thalassemia in order to permit an early time for diagnosis and to evaluate possible relation between myocardial iron overload and transfusion characteristics of the patients, as well as genotype, liver iron content and serum ferritin level.

METHODS

A cross sectional study was carried on 100 patients (55 males, 45 females) with thalassemia, who had their follow up visits at pediatric hematology clinic of Zagazig University Hospital from May 2017 to April 2019. Total number of patients attended pediatric hematology outpatient clinic of Zagazig University Hospital during two years study period and fulfilled inclusion criteria were included as a comprehensive sample. Approval for performing the study was obtained from Pediatrics and Radiodiagnosis Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB)

approval and also informed written consent was taken from patients and/or their caregivers.

This Work was performed according to the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria involved patients from either sex who were above six years with beta thalassemia whether major or intermediate. Patients were excluded if they had other forms of chronic hemolytic anemia. According to β-globin gene synthesis, patients were arranged into three groups. Group one involved 34 patients (34%) where β-globin chain was not synthesized (β0β0 genotype), group two involved 16 patients (16%) where β-globin chain was synthesized in a small amount (β0β+ genotype) and group three involved 50 patients (50%) where β-globin chain was synthesized in a moderate amount (β+β+ genotype).

Our patients were subjected to: (a) Full medical history and detailed physical examination. (b) Routine investigations e.g. CBC, organ functions tests and serum ferritin. (c) Genotype was detected by DNA sequencing techniques in Laboratory of Hemoglobinopathies (University of Ulm, Ulm, Germany). A total of 100 peripheral blood EDTA samples from all individuals were collected. Genomic DNA was extracted from peripheral blood lymphocytes using a standard protocol. Beta-globin gene mutations were further characterized by direct DNA sequencing. (d) MRI heart and liver to detect myocardial and hepatic iron burden. Value of cardiac T2* above 20 ms was normal, mild cardiac iron burden was considered if cardiac T2* value was between 15-20 ms, moderate cardiac iron burden was between 10-15 ms and severe cardiac iron burden was considered if cardiac T2* value was less than 10 ms. Mean hepatic iron burden less than 3 mg/g dw was normal, 3–7 mg/g dw considered mild hepatic iron burden, 7–14 mg/g dw considered moderate hepatic iron burden and more than 14 mg/g dw considered severe hepatic iron burden[6].

Protocol of MRI

1. Preparation of patients: All magnetic resonance techniques were done by a 1.5-Tesla highly conducting magnet (Achieva). Fasting was not necessary before the examination. Also, sedation was not needed. Trigger of respiration was used to establish minimal movement.

2. Protocol: The technique was done while patient in the supine position. The extent of examination was from level of the lower trachea to the lower edge of the kidney. Gating of the heart was done for all patients using ECG. MRI protocol in our unit takes nearly forty min. Cardiac T2* performed at eight separate echo times (TE) using mid ventricular view plane. Liver T2* consists of five cuts passed through the middle of the liver in a single breath done at 15 distinct TE to allow sensitive measurement of hepatic T2* in patients who had mild hepatic iron concentration.

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS version 20 (IBM SPSS, Armonk, NY, USA) and Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA). Continuous variables were expressed as the mean ± SD and the qualitative variables were expressed as a number (percentage). X2 test, t test, ANOVA and correlation coefficient tests were used when appropriate. P-value < 0.05 was considered statistically significant, p-value < 0.001 was considered highly statistically significant, and p-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

The mean age of the patients was 13.6 years. They were 55 males (55%) and 45 females (45%). The mean serum ferritin was 2841.9 ng/ml. Demographic, transfusion and chelation data are presented in (table 1).

The mean content of hepatic iron was 14.4 mg/g dw and mean cardiac T2* was 28.2 ms. The data are presented in (table 2).

Older patients, those with early and frequent transfusions were at a great risk for myocardial siderosis. The data are presented in (table 3).

Myocardial siderosis was significantly higher in patients with β0β0 genotype in comparison

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to β0β+ and β+β+ genotypes. The data are presented in (table 4).

Highly significant negative correlation was detected between cardiac T2* value and serum ferritin. The data are presented in (figure 1).

Highly significant negative correlation was detected between cardiac T2* value and liver iron content. The data are presented in (figure 2).

Highly significant positive correlation was detected between serum ferritin and each of hepatic iron burden and patient age. While the age of the start of transfusion and transfusion frequency had highly significant negative correlation with serum ferritin. The data are presented in (table 5).

Tables and figures

Table (1): Demographic, transfusion, chelation characteristics and serum ferritin of patients.

Demographic Data	N= 100	
Age (years) Mean± SD (Range)	**13.6 ± 3.7**	**(6-23)**
Gender (n, %)		
Males	**55**	**(55)**
Females	**45**	**(45)**
Transfusion Data		
Mean± SD (Range)		
Age of start (months)	**9.9 ± 11.2**	**(3 – 84)**
Frequency (weeks)	**3.9 ± 3.8**	**(2 – 24)**
Chelation Data		
Age of start (years)		
Mean± SD (Range)	**2.6 ± 1.7**	**(2 – 8)**
Type (n, %)		
DFX	**53**	**(53)**
DFP	**17**	**(17)**
DFO	**9**	**(9)**
DFO+DFX	**3**	**(3)**
DFO+ DFP	**2**	**(2)**
No	**16**	**(16)**
Compliance (%) Mean± SD (Range)	**67.8 ± 36.1**	**(25 – 100)**
Serum Ferritin (ng/ml) Mean± SD (Range)	**2841.9 ± 2050**	**(900 – 7430)**

SD: Standard deviation; DFX: Deferasirox; DFP: Deferiprone; DFO: Desferrioxamine; ng: nanogram; ml: milliliter.

Table 2: Liver iron content and cardiac T2* in our patients.

LIC (mg/g dw) **Mean ± SD (Range)** **Median**	**14.4 ± 10.7 (1.1 – 37.2)** **16**
T2* (ms) **Mean ± SD (Range)** **Median**	**28.2 ± 8.6 (11.8 – 43.9)** **26**

LIC: Liver iron content; T2* indicates myocardial iron overload, SD: Standard deviation; dw: dry weight, mg: milligram; g: gram; ms: milliseconds.

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Table 3: Relationship between myocardial iron overload and demographic and transfusion characteristics in our patients.

	T2* (ms) Mean ± SD	Test	P
Demographic data			
Age (years)			
≤15	**30.1 ± 8.1**	**t = 4.1**	**<0.001**
>15	**22.5 ± 7.9**		
Gender			
Male	**27.2 ± 8.3**	**t=1.3**	**0.18**
Female	**29.5 ± 9**		
Transfusion data			
Age of start(months)			
≤10	**27.2 ± 8.6**		
>10	**35.1± 5.3**	**t =3.2**	**0.0017**
Frequency(weeks)			
≤ 5	**26.1 ± 9.1**		
>5	**31.9 ± 6.4**	**t=12.04**	**0.002**

T2* indicates myocardial iron overload, SD: Standard deviation.

Table 4: Relationship between myocardial iron overload and genotypes in our patients (based on beta chain production).

	β0β0 (N = 34)	β0β+ (N = 16)	β+β+ (N=50)	F	P
T2* (ms) Mean± SD	**22.3±7.6**	**26.6±6.5**	**32.9±7.2**	**21.8**	**<0.01**

T2* indicates myocardial iron overload, SD: Standard deviation.

Table 5: Correlation between serum ferritin and other parameters.

	r	P	Significance
Age (years)	**0.43**	**< 0.001**	**HS**
Age of start transfusion (months)	**-0.56**	**<0.001**	**HS**
Frequency (weeks)	**-0.58**	**<0.001**	**HS**
LIC (mg / g dw)	**0.79**	**<0.001**	**HS**

LIC: Liver iron content; dw: dry weight, mg: milligram; g: gram; HS: Highly significant.

Figure 1: Correlation between serum ferritin and cardiac T2*.

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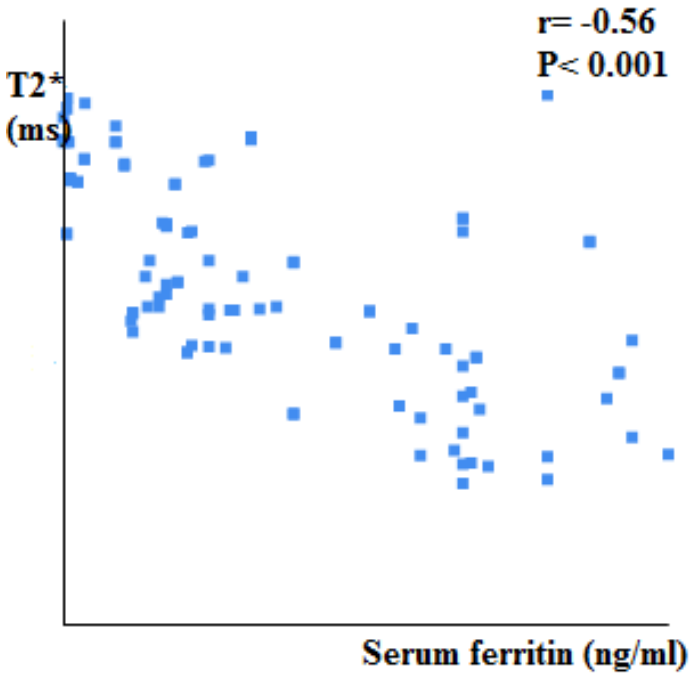
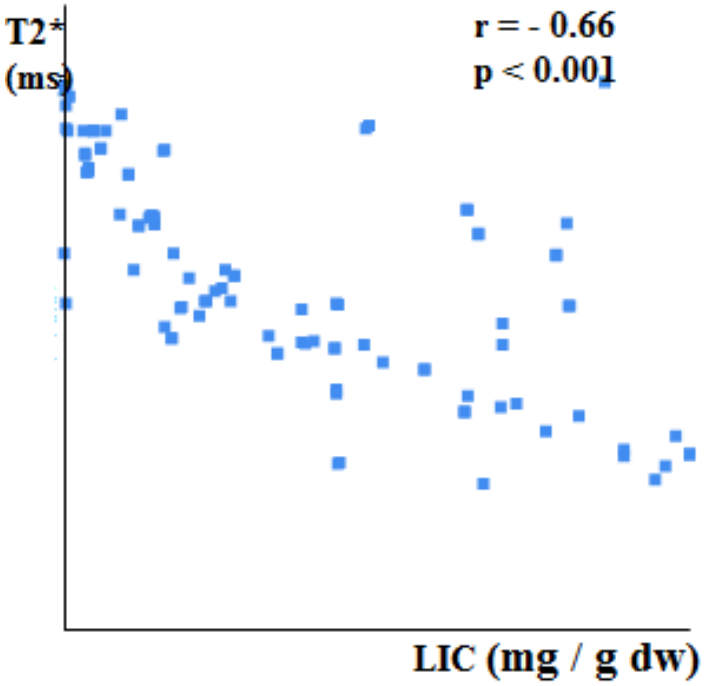


T2* indicates myocardial iron overload, ng: nanogram; ml: milliliter.

Figure (2): Correlation between Liver iron content and cardiac T2*.



LIC: Liver iron content; dw: dry weight, mg: milligram; g: gram; ms: milliseconds, T2* indicates myocardial iron overload , ms: milliseconds.

DISCUSSION

In thalassemia, iron overload occurs as result of both frequent blood transfusion and enhanced iron absorption from the gut **[7]**. A cardiomyopathic change induced by myocardial siderosis is a critical problem and considered the major etiology of death in thalassemia major patients [8]. Cardiac T2* is considered effective tool for evaluation of cardiac function and detection of myocardial siderosis **[9]**. In our study, the mean patient's age was 13.6 years. The males were 55% of our patients. The mean age of transfusion beginning was 9.9 months and the mean of

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transfusion frequency was every 3.9 weeks. The mean age of chelation beginning was 2.6 years. Deferasirox was the most commonly used medication for iron chelation. The mean compliance was 67.8 % and the mean serum ferritin was 2841.9 ng/ml.

This male predominance was also reported in Salama et al. **[10]** in their study in Mansoura Children's Hospital, Egypt, they found that 56.6% of the patients were males.

Ismail et al. **[11]** in their study on Malaysian thalassemia children found similar results regarding transfusion frequency where 66% of their patients required monthly blood transfusion. Unlike our study, they found that Desferrioxamine was the most common used iron chelator by 70% of their patients.

In our study, the mean liver iron content was 14.4 mg/g dw and mean cardiac T2* was 28.2 ms. Similarly, Wood et al. **[12]** in their study on patients with transfusion dependent thalassemia major with a mean age 15.7 years, they found that mean liver content and mean cardiac T2* values were 18.4 ± 3.8 mg/g dw and 26.1 ± 4.6 ms respectively. On the contrary, Casale et al., **[13]** in their study on 107 pediatric patients with thalassemia major (age <18 years), found that mean hepatic iron content and mean cardiac T2* values were 7.3 mg/g dw and 32.8 ms respectively.

In our study patients with age > 15 years, those with earlier and more frequent transfusion had lower cardiac T2* levels than those with age ≤ 15 years, those with delayed and less frequent transfusion. Risk of myocardial siderosis was nearly equal between males and females.

Similarly, Marsella et al. **[14]** found that cardiac T2* value was nearly similar without statistically significant difference between males and females (24 ms versus 26 ms for males and females respectively. Similarly, Di Tucci et al. **[15]** found that cardiac T2* correlated with transfusion requirements (p =0.0002) where pathological T2* values were not observed except if patients had received overall packed RBCs transfusion more than 290 ml/ kg.

On the contrary, Wahidiyat et al. **[16]** in their study over 162 thalassemia major patients found that cardiac T2* was not affected by age.

In our study highly significant negative correlation was detected between cardiac T2* value and liver iron content (r=-0.66, p<0.001).

On the contrary, Farhangi et al., [8] found that cardiac T2* value was not affected by liver iron content which was attributed to the difference in cellular iron transport and deposition in these organs.

In our study highly significant negative correlation was detected between cardiac T2* value and serum ferritin (r=-0.56, p<0.001).

In agreement with our study, Farhangi et al., [8] showed that there was strong negative correlation between cardiac T2* and serum ferritin (r = -0.347, p < 0.0001). On the contrary, khaled et al. **[17]** in their study over 40 thalassemia major patients observed that serum ferritin had inverse weak correlation with cardiac T2* (p = 0.013).

In our study, β0β0 genotype was the most aggressive genotype as regard to the development of myocardial siderosis in comparison to β0β+ and β+β+ genotypes where mean cardiac T2* was significantly lower in β0β0 genotype in comparison to β0β+ and β+β+ genotypes (22.3, 26.6 and 32.9 ms respectively).

Similarly, Hassan et al. **[18]** in their study over 73 thalassemia patients observed that the mean cardiac T2* value was significantly lower in β0β0 compared to β0β+ and β+β+ genotypes (21.3, 26.6 and 33.1 ms respectively).

In our study, highly significant positive correlation was detected between serum ferritin and each of hepatic iron burden and patient age. While the age of start of transfusion and transfusion frequency had highly significant negative correlation with serum ferritin.

Similarly, Majd et al. **[19]** in their study on 85 thalassemia patients observed that serum ferritin level had strong positive correlation with hepatic iron burden (r = 0.718, P < 0.001).

On the contrary, Azarkeivan et al. **[20]** in their study on 156 thalassemia major patients observed that there was weak correlation between serum ferritin and hepatic iron

burden (r = 0.535). Also, Eghbali et al. **[21]** in their study on 60 beta thalassemia patients observed that patient age and rate of blood transfusion were not indicators for serum ferritin.

The study had some limitations including small sample size and being a cross sectional study which is susceptible to misclassification.

We recommend assessment of myocardial iron overload using cardiac T2* which is simple, non-invasive, reliable and sensitive method on a large scale multicenter study. Also, we recommend early genetic study for patients with beta thalassemia which is helpful for prediction of myocardial siderosis and in planning of early intervention strategies.

CONCLUSION

Myocardial iron overload was a critical problem in beta thalassemia major patients with a clear association with genotype, serum ferritin and liver iron content.

- Conflict of Interest: None.
- Financial Disclosures: None.

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