β-Thalassemia intermedia: morbidity uncovered

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Magnetic Resonance Evaluation Of Hepatic And Myocardial Iron Deposition In Transfusion-independent Thalassemia Intermedia Compared To Regularly Transfused Thalassemia Major Patients

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Annals of Hematology 2010;89:585-589

Absence of cardiac siderosis despite hepatic iron overload in Italian patients with thalassemia intermedia: an MRI T2* study

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Received: 27 October 2009 / Accepted: 1 December 2009 / Published online: 17 December 2009

Abstract Cardiac involvement in patients with thalassemia intermedia (TI) is characterized by a high-output state and pulmonary hypertension, with systolic left ventricle function usually being preserved. Myocardial iron overload in patients with TI has not been extensively studied. We conducted a cross-sectional study of 49 Italian patients with TI. Patient charts were reviewed and data collected for transfusion and iron chelation history, status of the spleen, and comorbid illnesses or infections. Blood samples were obtained for assessment of hemoglobin, serum ferritin, and liver enzyme levels. Doppler echocardiography was done for all patients. Cardiac and hepatic iron levels were measured by magnetic resonance imaging T2*. The mean age was 40.5±8.3 years, with a male to female ratio of 29:20. A total of 34 (69.4%) patients were splenectomized, and four patients had evidence of hepatitis C infection. Around 45% of patients were transfusion naïve while the rest received infrequent (47%) or regular (8%) transfusions. A total of 31 (63.3%) patients were maintained on iron chelation therapy. None of the patients had evidence of heart failure. Mean serum ferritin and liver iron concentration were 1,060.2 ng/ml and 8.2 mg Fe per gram dry weight, respectively. None of the patients had evidence of cardiac iron overload (mean cardiac T2*=38.7±11.0 ms). There were no statistically significant correlations between cardiac T2* values and liver iron concentration, serum ferritin, or any patient, disease, or treatment-related parameters. Patients with TI show absence of cardiac iron overload even if hepatic iron accumulation is significant.

Keywords Thalassemia intermedia · Iron overload · Heart · Liver · Magnetic resonance imaging

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Introduction

In contrast to thalassemia major (TM), patients with thalassemia intermedia (TI) often have mild anemia that generally does not require regular blood transfusion therapy until later in life. However, TI patients remain at risk of the clinical sequelae of iron overload, primarily due to increased intestinal iron absorption and ineffective erythropoiesis [1]. Heart disease is the primary cause of death in TM, with myocardial iron loading observed in approximately two thirds of patients receiving iron chelation therapy [2]. In TI, cardiac involvement is mainly characterized by a high-output state and pulmonary hypertension, with systolic left ventricle function usually being preserved

[3, 4]. Myocardial iron overload in patients with TI has not been extensively studied; however, a recent report has shown no evidence of cardiac iron in a small group (n=20) of patients [5]. The current study aims to further evaluate cardiac iron overload in a larger group of TI patients and explore its correlation with liver iron concentration (LIC) and serum ferritin (SF) levels among other patient and disease characteristics.

Materials and methods

This was a cross-sectional study of patients with TI treated at the Centro Anemie Congenite, Ospedale Maggiore Policlinico, IRCCS, University of Milan, Milan, Italy. All patients were diagnosed with TI based on criteria previously described [6, 7]. This study recruited adult patients only to avoid the need for sedation to complete the magnetic resonance imaging (MRI) in children. Out of a cohort of 124 patients registered at the center, 49 adults (≥18 years) were identified. Patient charts were reviewed for data on patient's demographics (age and gender), splenectomy status, presence of comorbid illnesses or infections, and history of transfusion and iron chelation therapy. For transfusion status, patients were divided as follows: regularly transfused (two to four times per year), infrequently transfused (few transfusions received in the past), and transfusion naïve. Iron chelation therapy had to be administered for at least 1 year or else the patient was considered nonchelated. Written informed consent was provided by all patients, and approval was obtained from the ethical committee at the center.

Laboratory tests

Blood samples were obtained for assessment of pretransfusion hemoglobin (Hb), steady-state SF, and alanine transaminase (ALT) levels.

Echocardiography

Doppler echocardiography to assess left ventricular ejection fraction (LVEF) was done.

Magnetic resonance imaging

Cardiac iron levels were measured by MRI T2*. Patients were scanned with MRI 1.5 T Magnetom Avanto Siemens using a multiecho breath-hold sequence (echo times (TE) 2.58–18·9 ms) as described by Wood [8]. In this study, cardiac T2* >20 ms was considered normal. LIC was calculated from liver T2* images (TE 0.99–16.50 ms) according to the formula $[1/(\mathrm{T2}^*/1{,}000)] \times 0.0254 + 0.202]$ [9]. All T2* images were analyzed using postprocessing software (CMR Tools, Imperial College, London).

Statistical analysis

Data are expressed as means ± standard deviation (SD) or percentages where appropriate. All univariate comparisons between iron overload parameters (SF, LIC, and cardiac T2*) and continuous variables (age, Hb, LVEF, ALT) were evaluated using Spearman's (r_s) correlation coefficients. Comparisons with categorical variables (gender, splenectomy, transfusion, and chelation status) were evaluated using the independent samples t test and analysis of variance (ANOVA) test. A multivariate stepwise regression analysis was done to determine significant correlations. Linear regression analysis was performed to study correlations between SF, LIC, ALT, and cardiac R2* values ($\mathrm{R2}^* = 1{,}000/\mathrm{T2}^*$). All P values are two sided with the level of significance set at <0.05.

Results

Data from 49 patients were included in this analysis (Table 1). A total of four patients had evidence of hepatitis C virus (HCV) infection confirmed by polymerase chain reaction RNA testing. Among patients who received iron chelation therapy, 29 (93.5%) were maintained on subcutaneous deferoxamine regimens (20–60 mg/kg for 12 h a day, 3 days a week) while two (6.5%) received the oral iron chelator deferasirox (15–20 mg/kg/day). No patient had evidence of heart failure by modified Framingham criteria [10].

The mean ± SD of SF levels and LIC were 1,060.2± 1,090.3 ng/ml (range: 165–6,361 ng/ml) and 8.2±6.0 mg Fe per gram dry weight (dw; range: 1.1–26.4 mg Fe per gram dw),

Table 1 Patients' characteristics

Parameter	Value
Mean age ± SD, years (range)	40.5±8.3 (23–64)
Male/Female	29/20
Splenectomized, *n* (%)	34 (69.4)
Transfusion status, *n* (%)	
Naïve	22 (44.9)
Infrequent	23 (46.9)
Regular	4 (8.2)
Chelation received, *n* (%)	31 (63.3)
Mean ALT ± SD, IU/L (range)	36.2±23.5 (9–91)
Mean Hb ± SD, g/dL (range)	8.8±1.5 (5.3–13.1)
Mean LVEF ± SD, % (range)	65.8±4.9 (57–79)

ALT alanine transaminase, *Hb* hemoglobin, *LVEF* left ventricular ejection fraction

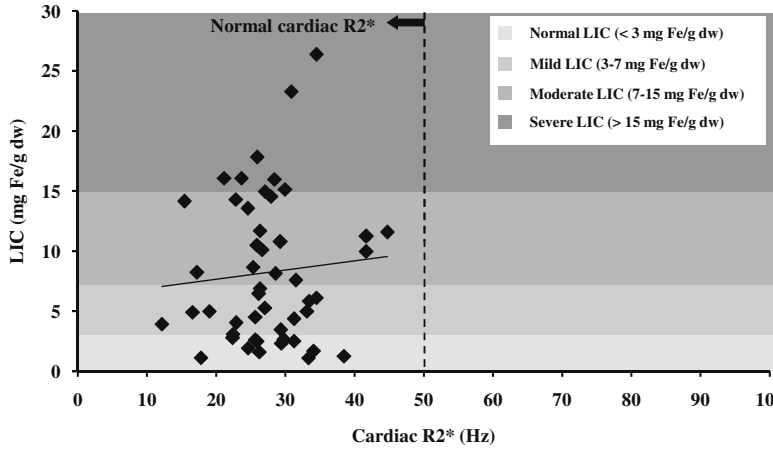

Fig. 1 Correlation between liver iron concentration (*LIC*) and cardiac R2* values

respectively. None of the patients had evidence of cardiac iron overload (mean cardiac T2* = 38.7 ± 11.0 ms; range: 22.4–82.4 ms). On linear regression analysis, there were no statistically significant correlations between cardiac R2* and LIC (R^2=0.007; P=0.569; Fig. 1) or SF (R^2=0.003; P=0.716). There was a statistically significant positive correlation between SF and LIC but with poor linearity (R^2=0.435; P=<0.001).

Table 2 Univariate analysis showing correlations between study variables and iron overload parameters

Variable	SF (ng/mL)	LIC (mg Fe per gram dry weight)	Cardiac T2* (ms)
Categorical[a]			
Gender			
Male (n=29)	1,132.9±1,285.9	7.6±5.8	40.8±11.8
Female (n=20)	943±685.3	9.2±6.4	35.6±9.3
P value	0.567	0.375	0.107
Splenectomy			
Yes (n=34)	1,264.1±1235.4	8.5±5.9	40.2±12.5
No (n=15)	579.4±308.2	7.7±6.6	35.3±5.9
P value	0.048	0.691	0.157
Transfusion status			
Naïve (n=22)	642.3±685.3	6.3±5.0	37.4±5.9
Infrequent (n=23)	1,341.7±1,265.0	10.0±6.7	41.1±14.5
Regular (n=4)	1,826.3±1191.0	9.1±5.8	32.4±6.7
P value	0.044	0.115	0.270
Iron chelation			
Yes (n=31)	1313.8±1233.8	9.1±6.5	38.9±11.8
No (n=18)	612.5±570.0	7.7±6.6	38.4±10.0
P value	0.033	0.220	0.895
Continuous[b]			
Age (years)	0.2	−0.023	−0.196
P value	0.178	0.878	0.177
Hb (g/dL)	−0.103	−0.129	0.003
P value	0.489	0.377	0.986
ALT[c] (IU/L)	0.600	0.421	−0.039
P value	<0.001	0.004	0.801
LVEF (%)	0.109	−0.129	0.003
P value	0.464	0.377	0.986

SF serum ferritin, *LIC* liver iron concentration, *Hb* hemoglobin, *ALT* alanine transaminase, *LVEF* left ventricular ejection fraction

[a] Statistical correlation evaluated by the independent samples t test and ANOVA test; data presented as mean ± SD

[b] Statistical correlation evaluated by Spearman's correlation; data presented as Spearman's correlation coefficient (r_s)

[c] Excluding the four patients with hepatitis C infection

SF levels were significantly higher in splenectomized, regularly transfused, and chelated patients and correlated positively with ALT levels (Table 2). On multivariate analysis, only ALT levels retained correlation with SF levels ($P<0.001$). Similarly, LIC values were only significantly positively correlated with ALT levels (Table 2). However, ALT levels did not rise linearly with SF ($R^2=0.371$) or LIC ($R^2=0.127$). There was no statistically significant correlation between cardiac T2* values and any of the study parameters (Table 2).

Of note, there was no statistically significant differences between HCV-positive and HCV-negative patients with regards to SF ($P=522$), LIC ($P=603$), or cardiac T2* ($P=534$); however, HCV-positive patients had higher mean ALT levels than HCV-negative patients (58.8 vs. 34.1 IU/L; $P=0.043$).

Discussion

Data from this cross-sectional study show absence of cardiac iron overload in patients with TI, despite significant hepatic iron accumulation (>7 mg Fe per gram dw), thus providing additional insight to aid our understanding of iron deposition in this patient group.

These data, which show cardiac T2* within the normal range in all patients, support other recent findings in which cardiac T2* was >20 ms in 20 never or minimally transfused TI patients despite elevated LIC [5]. Furthermore, they are consistent with studies showing that patients with TI are generally less prone to the cardiac iron overload associated with morbidity and mortality than patients with TM [4]. However, they contrast with other reports indicating moderate cardiac iron overload in subgroups of TI patients [11, 12]. The varying results might be explained by differences in baseline characteristics (e.g., previous transfusion history and copathology) between patient populations.

In TI, the combination of ineffective erythropoiesis and chronic anemia/hypoxia results in hepcidin suppression, increased intestinal iron absorption, and increased release of recycled iron from the reticuloendothelial (RE) system (macrophages) to the hepatocytes [1, 13, 14]. This explains the relatively low levels of SF yet high LIC (regardless of transfusion history) and confirms that SF underestimates iron burden in TI with poor correlation with LIC [15, 16]. By contrast, in transfused TM patients, iron is preferentially distributed to the RE system, stimulating SF synthesis and its release to the circulation [15]. The effect of this disparity in the pathophysiology of iron overload on cardiac sparing in TI patients and the probability of eventual cardiac iron overload with continuous transfusion therapy merits consideration in long-term follow-up studies.

In fact, the relationship between cardiac T2* values and iron balance is quite complicated because the mechanisms and kinetics of cardiac iron uptake and clearance differ from the liver [17, 18]. The lack of correlation between cardiac T2* and LIC or SF in the current study is consistent with data from a previous study on TI patients in which the authors found no correlation between cardiac T2* and SF values [5]. Data from animal models of iron overload in TI also indicate early accumulation of iron in the liver, with accumulation of iron in the heart occurring over longer periods [19]. Studies on patients with TM and sickle cell disease (SCD) confirm that cardiac T2* values do not correlate with SF concentration and LIC in cross-sectional analysis, while longitudinal studies continue to imply a causal relationship [12, 17, 18, 20–22]. Wood and Noetzli [17, 20] demonstrated a significant latency to cardiac T2* changes, relative to liver accumulation, suggesting a long delay between poor iron control and detectable cardiac iron deposition. Other MRI work suggests that a “critical” liver saturation is necessary to achieve positive cardiac iron balance [23]. This may explain absence of cardiac iron overload even in patients who had LIC >15 mg Fe per gram dw in this study.

In conclusion, in patients with TI who had or had not received previous transfusion therapy, we found no evidence of cardiac iron overload although hepatic iron accumulation was significant. Further research is needed to better understand if (and when) detectable cardiac iron deposition can occur in patients with TI. Data also confirm that SF levels do not accurately reflect the level of iron overload. Thus, recommendations for the management of patients with TI should include regular assessment of LIC via biopsy or noninvasive imaging methods, with iron chelation therapy being initiated in patients with LIC levels indicating liver iron overload.

Conflict of interest MDC and ATT are members of Novartis Speakers' Bureau. JCW received research funding from Novartis Pharmaceuticals.

Funding This study did not receive external funding.

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