β-Thalassemia intermedia: morbidity uncovered

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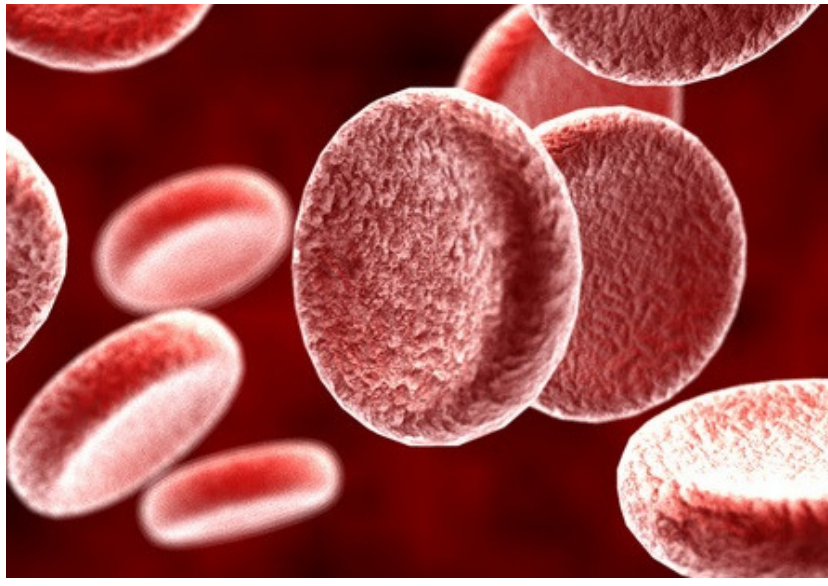

Magnetic resonance evaluation of hepatic and myocardial iron deposition in transfusion-independent thalassemia intermedia compared to regularly transfused thalassemia major patients

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Extremely diverse phenotypes exist within the homozygous and compound heterozygote states for β-thalassemia. The terms thalassemia major (TM) and intermedia (TI) lack specific molecular correlates, but encompass a wide spectrum of clinical and laboratory abnormalities [1]. At the severe end of the spectrum are patients whose clinical course is characterized by profound anemia, who present to medical attention in the first year of life, and who subsequently require regular transfusions for survival, the condition known as TM. But many patients with inheritance of two mutant beta alleles have a milder illness, with a broad range of severity including, at least in early childhood, a virtually asymptomatic state. Patients in this group who present to medical attention in later childhood and remain largely transfusion free are said to have TI [1]. The pathophysiology, clinical consequences, and treatment of iron overload in regularly transfused patients with TM have been extensively studied; however, in transfusion-independent patients with TI data remain limited. Recent advances in the assessment of organ-specific iron deposition using magnetic resonance imaging (MRI) are promising and could potentially aid understanding the pathophysiology of iron in patients with TI.

We evaluated 19 TI and 19 age- and sex-matched TM patients attending to the Chronic Care Center, Hazmieh, Lebanon. All patients were splenectomized. None of the patients had clinical signs of heart failure according to Framingham's modified criteria [2], and none had any history or echocardiographic evidence of cardiopulmonary disease including pulmonary hypertension. Moreover, none of the patients had a history of hepatitis B or C infection (by HB_s Ag and HCV RNA-PCR testing, respectively) or abnormal liver function (defined as alanine transaminase serum

TABLE I. Comparison of the Studied Parameters Between Thalassemia Intermedia and Major Patients (Independent Samples *t*-Test)

Parameter	Thalassemia intermedia, $n = 19$	Thalassemia major, $n = 19$	*P*-value
Mean age ± SD, years (range)	32.8 ± 7.9 (18–51)	33.0 ± 7.4 (17–49)	0.861
Male/Female	11/8	11/8	–
Mean Hb ± SD, g/dl (range)	8.9 ± 2.3 (4.9–13.1)	9.9 ± 1.6 (7.1–12.2)	0.241
Mean SF ± SD, ng/ml (range)	1316.8 ± 652.3 (460–3,157)	3723.8 ± 2568.8 (827–10,214)	0.001
Mean LIC ± SD, mg Fe/g dw (range)	15.0 ± 7.4 (3.4–32.1)	15.7 ± 9.9 (1.7–32.6)	0.095
Mean cardiac T2* ± SD, msec (range)	47.3 ± 7.1 (35.0–66.9)	21.5 ± 15.2 (5.1–50.7)	<0.001

Hb, hemoglobin; SF, serum ferritin; LIC, liver iron concentration; dw, dry weight.

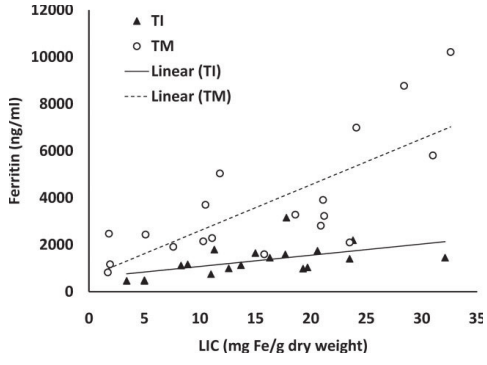

Figure 1. Linear regression analysis of serum ferritin (SF) versus liver iron concentration (LIC) in both thalassemia intermedia (TI) and major (TM) patients. In TI: SF = 583 + 42.6 × LIC; $R^2 = 0.43$; $P = 0.003$; standard error for the intercept is 202 and for the slope is 12.2 (there was one outlier excluded). In TM: SF = 642 + 196 × LIC; $R^2 = 0.57$; $P = 0.0002$; standard error for the intercept is 765 and for the slope is 41.5 (no outliers). The 95% confidence intervals for slope TI are [17.0–68.2] and for slope TM are [109–283]. As the error bars do not overlap, the slope differences are statistically significant. There are no differences in the intercepts.

level > 50 IU/l). All TI patients were transfusion and iron chelation naive, whereas all TM patients were regularly transfused (every 2–3 weeks) and iron chelated with desferrioxamine (started before the age of 7 years, in a daily dose of 30–50 mg/kg, given 5–6 times weekly). For all patients, blood samples were obtained for the assessment of hemoglobin (Hb) (pretransfusion in case of TM) and steady-state serum ferritin (SF) levels. Direct determination of liver iron concentration (LIC) was performed by R2 MRI using established methodology [3]. This technique has been widely validated in multicenter trials and independently verified [4]. 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) 5·6–17·6 msec] as described by Wood [4]. In this study, cardiac T2* > 20 msec was considered normal. The study received institutional review board approval, and all patients signed written informed consents.

Despite having comparable LICs, TI patients showed a statistically significant lower SF and higher cardiac T2* values (all TI patients had normal cardiac T2*) than patients with TM (Table I). Although the predictive power of SF for LIC was low in both TI and TM patients, SF had a statistically significant steeper (nearly fivefold) relationship with LIC in TM compared with TI patients (see Fig. 1). Extrapolating from the equations of the plots of LIC versus SF, for a similar SF, $LIC_{TI} = (4.1 \times LIC_{TM}) + 0.9$ mg Fe/g dry weight. Cardiac R2* (1000/T2*) values did not correlate with SF or LIC in both TM and TI patients.

Our study demonstrates that in transfusion-independent and nonchelated TI patients, LIC may be comparable to that of regularly transfused TM patients and surpass the recommended levels, highlighting that many patients with TI will be at risk of significant iron-related morbidity and mortality without the introduction of adequate chelation therapy. Data from this study show that isolated SF measurement has sufficient variability and hence poor predictability of LIC in both TI and TM patients. However, it appears particularly easy to underappreciate the severity of underlying iron overload when using SF in TI patients because the relationship between SF and LIC is so weak relative to background fluctuations in SF. Studies on patients with TI have consistently shown that SF levels are significantly lower than in patients with TM despite comparable levels of liver iron, which has significant implications on patient management and follow-up [5–7]. 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. This results in depletion of macrophage iron, relatively low levels of SF, and preferential portal and hepatocyte iron loading [5,7,8]. The situation in TI is similar to that seen in patients with hereditary hemochromatosis syndromes, which is characterized by impaired hepcidin production. By contrast, in transfused TM patients, iron is preferentially distributed to the macrophages in the RE system including the liver, stimulating ferritin synthesis and its release to the circulation, leading to high SF levels [7–9].

Despite significant hepatic siderosis, none of the TI patients showed evidence of cardiac iron loading in contrast to patients with TM. These data, which show cardiac T2* within the normal range in all patients, support other recent findings in which cardiac T2* was >20 msec in never or minimally transfused TI patients despite elevated LIC [10–12]. However, absence of evidence does not necessarily mean evidence of absence. The number of TI patients recruited in our study and previous reports remains small. In fact, cardiac iron deposition has been documented in small subgroups of older TI patients both through MRI evaluation [13,14] and as determined by endomyocardial biopsy [15]. Thus, similar to patients with hereditary hemochromatosis, untreated TI patients would most likely develop cardiac siderosis in middle age or as senior citizens. Moreover, accumulation of toxic iron species within myocytes is not necessary to induce cardiac dysfunction, and only initial exposure to nontransferrin-bound iron may be enough to cause damage to cardiac tissue. The latter entails that even without evidence of cardiac siderosis, TI patients may still be at risk of iron-related organ dysfunction secondary to hepatic iron overload with subsequent release of toxic species, thus highlighting the need for effective iron chelation therapy in this patient population [16–18].

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 [19]. The lack of correlation between cardiac T2* and LIC or SF in this study is consistent with data from a previous studies on TI patients in which the authors found no correlation between cardiac T2* and SF values [10–14]. Studies on patients with TM and sickle cell disease 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 [19]. It was demonstrated that there is a significant latency to cardiac T2* changes, relative to liver accumulation, suggesting a long delay between poor iron control and detectable cardiac iron deposition [20,21]. Other MRI work suggests that a "critical" liver saturation is necessary to achieve positive cardiac iron balance [22]. This may explain absence of cardiac iron overload even in TI patients who had LIC > 15 mg Fe/g dry weight in this study.

In conclusion, in patients with TI who had not received previous transfusion or iron chelation therapy, we found no evidence of cardiac iron overload although hepatic iron accumulation was significant. However, patients with TI, especially the elderly, should still be screened for evidence of cardiac siderosis until further research helps to better understand if (and when) detectable cardiac iron deposition can occur in patients with TI. Data also confirm that isolated SF levels do not accurately reflect the level of hepatic iron overload in TI or TM patients and can lead to significant underappreciation of the true burden of iron overload in transfusion-independent patients with TI. Thus, recommendations for the management of patients with TI should include regular assess-

ment of LIC via biopsy or noninvasive imaging methods, with iron chelation therapy being initiated in patients with LIC levels indicating liver iron overload.

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