Evaluation of the 5 mg/g Liver Iron Concentration Threshold and its Association with Vascular and Endocrine/Bone Morbidity in Beta-Thalassemia Intermedia

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Background

- Iron overload in transfusion-independent patients with beta-thalassemia intermedia (TI) primarily occurs through increased intestinal iron absorption.1
- Without treatment, TI patients continue to accumulate iron and ultimately attain considerably higher liver iron concentration (LIC) levels.2
- An association between elevated LIC and increased vascular and endocrine/bone morbidity in non-chelated patients with TI has been established.3
- Recently, data from the first randomized trial of iron chelation therapy in non-transfusion-dependent thalassemia (including TI) became available. The THALassa study showed that deferiprox therapy in these patients leads to significant reduction in LIC. A LIC of ≥5 mg/g dry weight (dw) was used as an inclusion criteria and indication to initiate therapy.4

Objectives

- The aim of this study was to evaluate the association between the LIC 5 mg/g dw threshold and vascular as well as endocrine/bone morbidity in TI patients. Such data will help understand the potential effect on morbidity from treating patients reaching LIC levels ≥5 mg/g dw.

Methods

- This was a cross-sectional study of TI patients treated at two centers in Beirut, Lebanon and Milan, Italy.
- We included all patients for whom LIC measurements were available (n=168).
- None of the patients were receiving iron chelation therapy at the time of LIC measurement.
- None of the patients had co-inheritance of a-thalassemia or determinants associated with increased γ-chain production.
- None of the patients were receiving fetal hemoglobin inducing agents at the time of LIC measurement.
- Data were retrieved for demographics, splenectomy status, transfusion history, and average total hepatic iron level of all measurements undertaken during the year of LIC measurement.
- For LIC, direct determination of iron burden was performed using R2 magnetic resonance imaging (MRI) in Beirut and R2* MRI in Milan using established methodologies, calibrated to mg/g of iron by dw in fresh liver biopsy specimens.

Results

- Data were also obtained for the occurrence of the following morbidities:
  - Vascular: thrombosis (compression ultrasonography, contrast venography or angiography evidence of thrombus) or pulmonary hypertension (PHT, a systolic pulmonary artery pressure greater than 35 mm Hg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of ≥2.8 m/sec AND exertional dyspnea without evidence of left heart disease).
  - Endocrine/bone: hypothyroidism (thyroid stimulating hormone >4.7 μIU/l and a free T4 <0.8 mg/dl) or osteoporosis (bone densitometry T-score ≤ −2.5 SD) or hypogonadism (males: >13 years, not yet Tanner B2 [i.e. prepubertal breast development] or >14 years requiring estrogen replacement therapy or >15 years with primary amenorrhea; males: >14 years, not yet Tanner G2 [i.e. prepubertal genital development] or on androgen replacement therapy or >17 years, not yet Tanner G4 [i.e. midpubertal genital development]).
- The mean age of patients was 35.2 ± 12.6 years (range: 8-66 years) including 72 (42.9%) men. Some 121 (72%) patients were splenectomized.
- The mean total hemoglobin level was 8.8 ± 1.6 g/dl. A total of 44 (26.2%) patients had never received transfusions since diagnosis, while the remaining patients had received occasional transfusions (e.g. during pregnancy, surgery, or infection) or more regular yet temporary transfusions during childhood (for growth retardation) or adulthood (for the management of specific complications).
- The mean LIC value was 8.4 ± 6.7 mg/g dw (range: 0.5-32.1 mg/g dw) with 70 (41.7%) patients having a LIC of <5 mg/g dw and 98 (58.3%) having a LIC of ≤5 mg/g dw.
- Patients with a LIC ≥5 mg/g dw had a significantly higher prevalence of all evaluated morbidities than patients with a LIC <5 mg/g dw (Figure 1).
- Patients with a LIC ≥5 mg/g dw also had a significantly higher prevalence of multiple morbidities than patients with a LIC <5 mg/g dw (Figure 2).
- The absolute morbidity risk increase attributable to the ≥5 vs. <5 mg/g dw threshold (84.7% minus 50.0% = 34.7%) was as high as that attributed to the ≥7 vs. <7 mg/g dw threshold (88.6% minus 53.9% = 34.7%); the latter being a historical prognostic threshold of increased morbidity in patients with beta-thalassemia major.
- To determine whether the observed association between LIC and morbidity is due to confounding factors (risk factors that can lead to both iron overload and morbidity), we constructed a multivariate logistic regression model and adjusted the association between LIC and morbidity for age, sex, total hemoglobin level, splenectomy status, and transfusion history.
- The unadjusted odds ratio for the ≥5 vs. <5 mg/g dw threshold with morbidity as the dependent variable was 5.53 (95% CI: 2.69-11.40).
- Upon adjustment, the odds ratio dropped minimally to 3.76 (95% CI: 1.62-8.71) indicating that the observed association is largely independent of such confounding effects.

Conclusions

- A LIC of ≥5 mg/g dw is independently associated with a considerably increased risk of vascular and endocrine/bone disease in patients with TI.
- Administering iron chelation therapy for patients exceeding this threshold is thus not only expected to lower LIC but may be associated with a reduction in the risk of serious morbidities that are often irreversible.

References