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Serum ferritin level and morbidity risk in transfusion-independent patients with β-thalassemia intermedia: the ORIENT study

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Similar to other forms of non-transfusion-dependent thalassemia, the diagnosis of β-thalassemia intermedia is associated with a state of iron overload.[1–3] This occurs in the absence of regular transfusion therapy and is primarily attributed to increased intestinal iron absorption signaled by ineffective erythropoiesis and low serum hepcidin levels.[4] Although iron accumulation in transfusion-independent β-thalassemia intermedia patients is slower than in regularly-transfused β-thalassemia major, recent evidence highlights that a considerable proportion of patients ultimately reach clinically significant levels that can cause serious morbidities after the age of ten years.[1–3] Accordingly, current management guidelines recommend initiating iron chelation therapy in β-thalassemia intermedia patients over ten years of age and in whom liver iron concentration has reached 5 mg Fe/g dry weight (dw) or over.[2,5,6] This threshold was primarily selected in the light of its established association with morbidity in

β-thalassemia intermedia patients,[7,8] as well as recent evidence on the efficacy and safety of iron chelation therapy in non-transfusion-dependent thalassemia (including β-thalassemia intermedia) patients for whom treatment was started at 5 mg Fe/g dw or over (THALASSA trial).[9,10] A liver iron concentration of 3 mg Fe/g dw was also used and this was the recommended threshold at which to interrupt iron chelation therapy and avoid overchelation.[2,5,6,9] When liver iron concentration measurement is unavailable, serum ferritin levels of 800 and 300 ng/mL can be used as an alternative to the 5 and 3 mg Fe/g dw liver iron concentration values, respectively,[2,5,6] as established in the THALASSA trial through correlation analysis between both iron overload indices.[11,12]

With this background in mind, the aims of this study were 3-fold. 1) To evaluate the association between serum ferritin levels (and the relevant thresholds of 300 and 800 ng/mL) and morbidity risk in chelation-naive patients with β-thalassemia intermedia since, unlike for liver iron concentration, such data for serum ferritin level are lacking. This could further support the use of such thresholds to guide management, especially when liver iron concentration measurement is not available. 2) To evaluate such an association in a longitudinal fashion and over an extended period of observation time as current evidence on the relationship between iron overload and morbidity in β-thalassemia intermedia primarily stems from cross-sectional studies. 3) To evaluate whether such an association is independent through proper adjustment for potential confounders.

This was a retrospective cohort study using data from five comprehensive care centers in the Middle East (Egypt, Iran, Lebanon, and Oman) and Italy. Age at diagnosis of at least two years and hemoglobin values maintained between 7 and 9 g/dL without the need for a regular transfusional regimen, with or without splenomegaly, were the main criteria to define the β-thalassemia intermedia phenotype at presentation. All patients had pure β-globin gene mutations [IVS-I-6 (T>C), IVS-I-5 (G>C), IVS-II-1 (G>A), or Codon 39 (C>T)]. The current study utilized a completely de-identified dataset. Data were collected as part of now completed clinical studies that were approved by the Institutional Review Board at the institutions involved. We retrieved data for all β-thalassemia intermedia patients attending the centers on 1st January 2000 and who were followed-up until 31st December 2010, death, or loss to follow up (11-year observation period). We excluded patients who received transfusion, iron chelation, or fetal hemoglobin induction therapy before or throughout the observation period. We also excluded patients who already had any of the evaluated morbidities at the start of the observation period.

For each patient, we retrieved annual serum ferritin and hemoglobin levels during the 11-year observation period (2000–2010, inclusive) that represented an average of measurements taken in one year of follow up. Serum ferritin levels were also categorized into three groups: ≤300, >300 to <800, and ≥800 ng/mL. The boundaries of these serum ferritin level groups are the recommended thresholds for tailoring iron chelation therapy in non-transfusion-dependent thalassemia patients including β-thalassemia intermedia.[2,5,6] Serum ferritin level was retrieved while patients were fasting and within the steady-state in the absence of fever or any infection. We also retrieved data on the occurrence of any morbidities during the observation period, which were uniformly defined across centers and screened annually or when relevant signs or symptoms developed (*Online Supplementary Table S3*).

Data were analyzed for 52 β-thalassemia intermedia patients who fulfilled the eligibility criteria. The mean age of patients at the start of the

observation period was 24.1±1.6 years (range 2–56 years) including 25 (48.1%) males. Thirty (57.7%) patients were splenectomized, all prior to the start of the observation period. The mean total hemoglobin level in the year 2000 was 9.1±0.2 g/dL (range 6.8–12.5 g/dL), which decreased minimally during the 11-year observation period to a mean of 8.8±0.2 g/dL (range 6.7–12 g/dL) in 2010 (absolute decrease 0.3 g/dL; percent decrease 3%). The mean annual percent decrease in total hemoglobin level was 0.3% (*Online Supplementary Table S1*). No patient died or was lost to follow up during the observation period. The mean serum ferritin level in the year 2000 was 513.2±51.2 ng/mL (range 17–1508 ng/mL) that steadily and significantly increased during the 11-year observation period to a mean of 1209±103 ng/mL (range 76–2981 ng/mL) in 2010 (absolute increase 695.8 ng/mL; percent increase 135.6%) (P<0.001) (Figure 1A and *Online Supplementary Table S2*). The mean annual percent increase in serum ferritin level was 9%. Consequently, the proportion of patients with a serum ferritin level 800 ng/mL or over increased over time (*Online Supplementary Figure S1*), and 36 (69.2%) patients had at least one serum ferritin level of 800 ng/mL or over during the observation period.

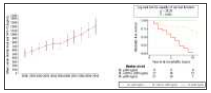

Figure 1.

(**A**) Annual mean serum ferritin level during the observation period. CI: confidence interval. (**B**) Kaplan-Meier survival curve with time to first morbidity by overall serum ferritin category. SF: serum ferritin level.

For all forthcoming association analyses, we used the average serum ferritin level during the 11-year observation period for each patient (termed hereafter overall serum ferritin level), and the mean for the whole group was 826.9±69.5 ng/mL (range 72–2065.6 ng/mL) with 8 (15.4%) patients having an overall serum ferritin level of 300 ng/mL or under, 17 (32.7%) over 300 to under 800 ng/mL, and 27 (51.9%) 800 ng/mL or over.

A total of 36 (69.2%) patients had at least one morbidity while 17 (32.7%) patients had multiple morbidities. The most common morbidities were osteoporosis (n=25, 48.1%), extramedullary hematopoiesis (n=10, 19.2%), and liver disease (n=9, 17.3%; none of the patients had concomitant hepatitis B or C infection); followed by hypothyroidism (n=5, 9.6%), hypogonadism and diabetes mellitus (n=4, 7.7% each), and thrombosis (n=3, 5.8%). Hypoparathyroidism and pulmonary hypertension were reported in one (1.9%) patient each.

The mean overall serum ferritin level was higher in patients with at least one morbidity than in those without any morbidity (Table 1). Upon exploring overall serum ferritin level categories, the cumulative incidence of at least one morbidity was 100% in patients with 800 ng/mL or over, 52.9% in patients with from over 300 to under 800 ng/mL, and 0% in patients with 300 ng/mL or under (P=0.001). Similarly, the cumulative incidence of multiple morbidities was 59.3% in patients with 800 ng/mL or over, 5.9% in patients with from over 300 to under 800 ng/mL, and 0% in patients with 300 ng/mL or under (P=0.001). The analysis was also stratified according to morbidity type, which confirmed the association between elevated serum ferritin level and morbidity in both patients with morbidity types primarily attributed to iron overload as well as those primarily and co-attributed to other factors (Table 1).

Table 1.

Stratification of the association between serum ferritin level and morbidity according to morbidity type.

Upon constructing Kaplan-Meier survival curves for time-to-first-morbidity by overall serum ferritin level category, it was apparent that the morbidity-free survival at ten years for patients with an overall serum ferritin level category of 800 ng/mL or over was 0% while it was 100% for patients with 300 ng/mL or under (log rank test *P*=0.001) (Figure 1B).

Figure 2 illustrates the incidence of morbidity for each patient as a function of age and serum ferritin level during the observation period. It was graphically apparent that morbidity primarily occurred as patients shifted to the higher serum ferritin level category (≥800 ng/mL). It was also apparent that with older and advancing age, patients had a higher incidence of morbidity, although they were also more likely to be in a higher serum ferritin level category (≥800 ng/mL).

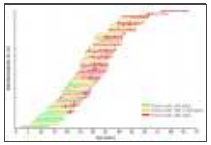

Figure 2.

Morbidity occurrence during the 11-year observation period presented as a function of age and serum ferritin level category. Each bar represents a single patient. The bar starts at the patient's base-line age, and represents serum ferritin level **...**

Accordingly, to evaluate whether the observed association between overall serum ferritin level and morbidity is independent of the effects of age and other potential risk factors, we constructed a Cox proportional hazard model (step-wise backward selection) with developing at least one morbidity and multiple morbidities as the dependent variables. Alongside overall serum ferritin level, the model included age at start of observation, sex, splenectomy status, and mean total hemoglobin level. Overall serum ferritin level was the only statistically significant variable associated with the occurrence of at least one morbidity (HR per 1 ng/mL increase: 1.002; *P*=0.001) as well as multiple morbidities (HR per 1 ng/mL increase: 1.011; *P*=0.005).

Our study strongly demonstrates that without iron chelation therapy, transfusion-independent patients with β-thalassemia intermedia continue to accumulate iron over time. It also echoes observations that mostly stem from cross-sectional studies, and confirms the damaging effects of iron overload in this patient population through a long-term cohort follow up. More importantly, our study supports the use of the 800 ng/mL or over threshold to initiate iron chelation therapy in β-thalassemia intermedia patients and the 300 ng/mL or under threshold to interrupt it.[2,5,6] These thresholds had previously been recommended based on their predictive power of liver iron concentration values used to initiate or interrupt iron chelation therapy (5 and 3 mg Fe/g dw, respectively).[11,12] Data from the current study further support their use based on their relationship with morbidity risk, where all patients with serum ferritin levels of 800 ng/mL or over, while none with levels 300 ng/mL or under, developed a

morbidity over this extended period of observation.

Collectively, this information should further guide decision-making concerning iron chelation, especially in resource poor countries where serum ferritin level is the only available tool for the assessment and monitoring of iron overload compared to other advanced techniques such as assessment of liver iron concentration by magnetic resonance imaging. Studies that evaluate the risk/benefit of initiating treatment in patients with a less conservative threshold (<800 ng/mL) would also be welcomed.

Footnotes

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