Iron overload in non-transfusion-dependent thalassemia

Khaled M. Musallam

*Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon;
Department of Medicine and Medical Specialties, IRCCS Ca' Granda Foundation Maggiore
Policlinico Hospital, University of Milan, Milan, Italy*

Abstract

Iron overload due to increased intestinal iron absorption remains a concern in patients with non-transfusion-dependent thalassemia (NTDT). A dynamic regulation between ineffective erythropoiesis and iron metabolism in these disorders has been recently elucidated. Although the rate of iron loading in NTDT is slower than that observed in regularly transfused patients, the process is cumulative and patients may reach considerably high liver iron concentration levels. The clinical consequences of iron overload in patients with NTDT are various and include hepatic disease, endocrinopathy, bone disease, and vascular outcomes; while cardiac siderosis is less frequently observed. Although serum ferritin levels correlate with LIC in NTDT, they underestimate iron load when compared with transfusion-dependent patients with equivalent LIC. Therefore, direct measurement of LIC is recommended to identify patients at risk and guide iron chelation decisions.

Introduction

Transfusion-dependence is an essential factor in characterizing the various phenotypes and their severity within the thalassemia syndromes. For instance, a diagnosis of β -thalassemia major entails life-long transfusion requirement for normal growth and development, and more importantly, survival. The main concern with transfusion-dependence is secondary iron overload, which if left untreated, leads

to target-organ toxicity and death (1). However, considerable advances have been attained, especially in the last decade, in iron overload assessment and management strategies for transfusion-dependent patients; which translated into improved patient outcomes (2-3). Non-transfusion-dependent thalassemia (NTDT) is a term used to label patients who do not require such regular transfusions for survival and encompasses several entities, the most prevalent of which are α -thalassemia (mainly HbH disease), hemoglobin E/ β -thalassemia, and β -thalassemia intermedia (4). Despite their transfusion-independence, patients with NTDT are still at risk of iron overload (5). Only recently, data on the mechanisms, consequences, and assessment of iron overload in NTDT started to emerge; and these will be herein reviewed.

Pathophysiology

Patients with NTDT may still require occasional blood transfusions; for example, in the case of poor growth or development during childhood, during infection or pregnancy, prior to surgery, or for the management of specific complications where the benefit of transfusion therapy has been established (6). Blood transfusions in NTDT patients, however, contribute much less to the total iron burden than they do in transfusion-dependent patients, and the main source of iron remains primary loading, similar to patients with hereditary hemochromatosis. The combination of ineffective erythropoiesis, anemia, and hypoxia leads to a compensatory increase in serum levels of erythropoietin, as well as a decrease in serum levels of hepcidin, which control the concentration of ferroportin on the intestinal epithelium (7). Proposed regulators of hepcidin production include growth differentiation factor-15 (GDF-15) (8-9), twisted gastrulation factor-1 (TWGF-1) (10), hypoxia inducible transcription factors (HIFs) (11), among others (12-13). Regardless of the signaling mechanism, the end result is suppression of hepcidin levels, increased intestinal iron absorption, and increased release of recycled iron from the reticuloendothelial system. This in turn leads to depletion of macrophage iron, relatively low levels of serum ferritin, and preferential portal and hepatocyte iron loading (14), with subsequent release into the circulation of toxic iron species (15). By contrast, regularly transfused patients do not have low hepcidin levels, and iron is preferentially distributed to the reticuloendothelial system, thereby stimulating ferritin synthesis and its release into circulation, resulting in high serum ferritin levels.

Iron overload in NTDT patients is a cumulative process as evident from studies documenting positive correlations between iron overload indices and advancing age (15-18). The accumulation of iron from intestinal absorption in NTDT patients is slower than that observed in transfusional siderosis and may reach 3-4 mg/day or as much as 1,000 mg/year (5). A mean annual increase in liver iron concentration (LIC) of 0.38 ± 0.49 mg Fe/g dry liver weight (dw) was observed in a recent trial including NTDT patients (19).

Correspondence: K.M. Musallam
E-mail: kmm06@mail.aub.edu

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Clinical consequences

A considerable proportion of NTDT patients eventually accumulate iron to LIC thresholds warranting concern (19-20). In the past five years, several observational studies, mostly from β -thalassemia intermedia patients (21), have confirmed an association between iron overload and morbidity in NTDT patients, further supporting the essential role of iron chelation therapy.

An association between iron loading evident from longitudinal elevations in serum ferritin level and worsening of hepatic fibrosis measures has been established (22). Several case reports and case series also suggest an association between iron overload and hepatocellular carcinoma in this patient population (23-25). Interestingly, studies using cardiac magnetic resonance imaging (MRI) did not observe cardiac siderosis even in NTDT patients with substantially elevated LIC (26-29). However, the number of patients recruited to these studies was small. Furthermore, cardiac siderosis has been documented in small subgroups of older NTDT patients through both MRI evaluation (30-31) and endomyocardial biopsy (32). Thus, the possibility that patients may develop cardiac siderosis later in life cannot be fully excluded. Moreover, damage to cardiac tissue may result from exposure to non-transferrin-bound iron (NTBI) without accumulation of toxic iron species within myocytes. This suggests that even without evidence of cardiac siderosis, NTDT patients may be at risk for iron-related cardiac dysfunction.

In a recent cross-sectional study of 168 patients with β -thalassemia intermedia, higher LIC values were associated with a significantly increased risk of developing thrombosis, pulmonary hypertension, hypothyroidism, hypogonadism, and osteoporosis (20). The LIC level associated with a significantly increased risk of developing vascular morbidity was ≥ 7 mg Fe/g dw, and the level for endocrine and bone morbidity was ≥ 6 mg Fe/g dw. These observations were made in both transfusion-naïve patients and in patients who received previous transfusions. Moreover, it was apparent that elevated LIC was associated with a steeper increase in the rate of age-related vascular morbidity and earlier onset of endocrine and bone disease compared with patients with low LIC (20). Recent studies have also documented a high prevalence of silent brain infarction, large cerebral vessel disease, and decreased neuronal function primarily in the temporal and parietal lobes in splenectomized adults with β -thalassemia intermedia (33-35). There was a significant association between the occurrence of large-vessel cerebrovascular disease and high NTBI levels (34), and decreased neuronal function was observed more frequently in patients with LIC >15 mg Fe/g dw (33).

Although the relationship between iron overload and hepatic or endocrine disease echoes evidence from transfusion-dependent β -thalassemia major patients, data on vascular outcomes remain novel. It should be noted that all relevant studies observed the association between iron overload and vascular outcomes after adjustment for age and several other disease-related risk factors, suggesting that the association is probably causal. However, further biological studies are needed to fully understand the mechanisms through which iron overload causes such pathology.

Assessment of iron overload

Direct assessment of LIC by biopsy or MRI is recommended in NTDT patients. Because MRI is widely available, it offers broad access to a reliable and noninvasive estimation of LIC. The reciprocals of T2 and T2*, named R2 and R2*, are directly proportional to LIC measured by biopsy (36-38). They are considered the gold standard for clinical trials and are FDA approved for clinical use. Measuring LIC using a supercon-

ducting quantum interference device is also possible (39); however, there is limited availability of this technology worldwide. Considering the slow kinetics of iron loading in NTDT, assessment of LIC need not start before patients reach 10 years of age, especially that the prevalence of iron-related morbidities in patients <10 years is low (16). Measurements can be done at one- or even two-year intervals (5), although closer monitoring may be needed to tailor therapy in patients eligible for iron chelation (LIC >5 mg Fe/g dw) (19). Although current evidence suggests that patients with NTDT are less likely to develop cardiac siderosis (26-29), cardiac MRI T2* assessment may still be warranted in older patients with high LIC.

Serum ferritin monitoring has been the method of choice in the clinic for many years because of its low cost and convenience; its positive correlation with transfusion burden, morbidity, and mortality in patients with β -thalassemia major; and because it allows longitudinal follow-up of patients. In NTDT patients, although serial measurement of serum ferritin levels to detect trends in iron loading and unloading is plausible, reliance on serum ferritin thresholds used to guide chelation therapy in β -thalassemia major (e.g., 1000 and 2500 ng/ml) is inappropriate. First, these thresholds were used in the transfusion-dependent population because of their association with morbidity and mortality in longitudinal studies (40), and similar reports in NTDT patients are lacking. Second, although there exists a positive correlation between serum ferritin level and LIC in NTDT patients (17-19, 39), the ratio of serum ferritin to LIC is lower relative to patients with β -thalassemia major (14, 17, 27, 39). Thus, spot measurements of serum ferritin level may underestimate iron overload in patients with NTDT if they are to be interpreted as with β -thalassemia major patients. Recommendations on the optimal serum ferritin thresholds to initiate or discontinue iron chelation therapy in NTDT patients should be soon available using data from the first clinical trial of an iron chelator in NTDT (THALASSA) (19).

Data on the use of other iron overload indices, such as transferrin saturation or NTBI, in NTDT patients are scarce, and no recommendations regarding their use in clinical practice can be made at this time.

Conclusions

Despite transfusion-independence, NTDT patients remain at risk of iron overload and related morbidity. Careful and timely assessment of iron burden can better identify patients at risk requiring iron chelation therapy. Future studies are expected to shed more light on the underlying pathophysiology of iron loading and the optimal approach to management.

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