Iron overload in patients with rare hereditary hemolytic anemia: Evidence-based suggestion on whom and how to screen

To the Editor:
Hereditary hemolytic anemia (HHA) encompasses a heterogeneous group of diseases characterized by premature destruction of the red cell. It can roughly be divided into 3 disease categories: hemoglobin disorders (eg, β-thalassemia, sickle cell disease [SCD]), red cell enzyme disorders (eg, pyruvate kinase deficiency, glucose-6-phosphate dehydrogenase deficiency), and red cell membrane disorders (eg, hereditary spherocytosis, hereditary xerocytosis).

Patients are at risk for iron overload due to blood transfusions or inappropriately high dietary iron absorption as a result of ineffective erythropoiesis. Excess iron can be stored in the liver, endocrine organs, and heart. Exposure of these organs to the toxic effects of iron causes organ damage and subsequent morbidity and mortality.

Iron overload has been extensively studied in β-thalassemia.1 However, data on the prevalence of iron overload in more rare forms of HHA is limited. In this study, we aim to evaluate the occurrence of iron overload in patients with rare HHA, and to determine the predictive value of ferritin and transferrin saturation (TSAT) levels to diagnose liver iron overload.

This cross sectional study included adult patients with rare HHA from who MRI results of the liver were available. Patients with SCD and β-thalassemia were enrolled as a reference group. The MRI (T2* or R2 MRI [Ferriscan]) threshold for liver iron overload was defined as LIC ≥ 3 mg ferritin per gram dry weight (mg/g) and for moderate to severe iron overload of LIC ≥ 7 mg/g. The MRI threshold for cardiac iron overload was defined as a <20 ms. For a detailed description of the methods we refer to the Supporting Information.

From February 2016 to June 2017 we included 44 patients with rare HHA. Median age at enrollment was 43 years (IQR 32-51), 20 patients (46%) were female. In total 17 patients (40%) had never received transfusions. Median Hb was 11.3 g/dL mmol/L (IQR 8.9-13.9). As a reference group, we included 86 patients with SCD and β-thalassemia. The MRI (T2* or R2 MRI [Ferriscan]) threshold for liver iron overload was defined as LIC ≥ 3 mg ferritin per gram dry weight (mg/g) and for moderate to severe iron overload of LIC ≥ 7 mg/g. The MRI threshold for cardiac iron overload was defined as a <20 ms. For a detailed description of the methods we refer to the Supporting Information.

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and β-thalassemia. Baseline characteristics are depicted in Supporting Information Table S1.

LIC ≥ 3 mg/g was present in 71% (31/44) of patients with rare HHA, LIC ≥ 7 mg/g was present in 36% (16/44) of patients and occurred in all forms of rare HHA included (Supporting Information Table S2). Of the patients who were never transfused 71% (12/17) did have LIC ≥ 3 mg/g, 18% (3/17) had LIC ≥ 7 mg/g. Of the patients who were sporadically transfused 65% (11/17) had LIC ≥ 3 mg/g and 41% (7/17) LIC ≥ 7 mg/g. Of the transfusion dependent patients this was 89% (8/9) and 67% (6/9). Patients with LIC ≥ 7 mg/g were more anemic than patients with LIC < 7 mg/g and their levels of plasma iron, ferritin, and TSAT were higher. (data not shown) Ferritin levels correlated to LIC in patients with rare HHA (ρ = 0.832, P ≤ .001, N = 40) (Figure 1A). Correlation was also seen within the never-transfused (ρ = 0.700, P = .004), sporadically transfused (ρ = 0.945, P ≤ .001), and transfusion dependent (ρ = 0.882, P = .002) subgroups. (Figure 1B) Despite this strong correlation, there was a poor sensitivity of ferritin levels >1000 ng/mL for LIC ≥ 7 mg/g (47%, Supporting Information Table S3). In total 25% (20/81) of patients with ferritin < 1000 ng/mL did have LIC ≥ 7 mg/g. Sensitivity for LIC ≥ 7 mg/g in never-transfused, sporadically transfused, and transfusion dependent patients was respectively 0%, 30%, and 67%. In the not-chelated, and never-transfused/not-chelated group it was respectively 11% and 0%. Decreasing the cut-off to 500 ng/mL again improved the sensitivity of ferritin for LIC albeit not to 100% in all groups.

TSAT did not correlate to LIC in patients with rare HHA. Of note, the 3 patients of the reference group with ferritin < 500 ng/mL and LIC ≥ 7 mg/g that had TSAT levels available, all had very high TSAT levels (85%, 88%, and 95% respectively). The sensitivity of ferritin > 500 ng/mL or TSAT > 45% for LIC ≥ 7 mg/g was 100% in all groups.

Cardiac MRI data was available for 33 patients with rare HHA. None had cardiac iron overload.

In the reference group, 7 patients had cardiac iron overload. All were transfusion dependent. One β-thalassemia patient with cardiac iron overload had ferritin levels of < 1000 ng/mL.

For 38 patients test results for hereditary hemochromatosis were available. There were no differences in LIC between patients heterozygous for either one of the HFE mutations, or between patients who carried a mutation vs patients that didn’t.

Our study shows that iron overload occurs in all forms of rare HHA included in this study. Importantly, it shows that iron overload is not limited to patients with ferritin levels > 1000 ng/mL or to patients with a history of transfusions. The results in rare HHA were very similar the results found in the reference group of patients with β-thalassemia and SCD.

Our study shows a correlation between ferritin and LIC; however, ferritin levels at a cut-off of 1000 ng/mL have a low sensitivity for iron overload. Iron overload detected by MRI in patients with ferritin levels < 1000 ng/mL occurred in all types of HHA studied, including patients that were never transfused. Therefore, a ferritin cut-off of 1000 ng/mL cannot be safely applied to patients with HHA. We recommend that MRI LIC measurement should be performed in all patients. Recently, in a study in non-transfusion dependent thalassemia patients, a ferritin cut-off of 800 ng/mL was demonstrated to have the best predictive value for iron overload (defined as LIC ≥ 5 mg/g) when MRI is unavailable.² Both in our rare HHA sample and in the reference group, the sensitivity of a cut-off of 800 ng/mL for LIC ≥ 7 mg/g remained poor. Notably, our reference group did not include never-transfused β-thalassemia patients. At a ferritin threshold of 500 ng/mL, sensitivity for LIC ≥ 7 mg/g increased to 100% in rare HHAs and increased to ≥ 67% in the reference group.

We did not find a correlation between TSAT and LIC in patients with rare HHA. Ideally, to interpret TSAT measurements, patients should withhold iron chelation for at least 1 day before measurement, as the presence of iron chelation in the bloodstream may influence the results.³ Notably, patients with LIC ≥ 7 mg/g, despite low ferritin levels, did have very high TSAT levels suggesting that TSAT may be helpful in recognizing patients with iron overload despite a low ferritin. It could be interesting to repeat these measurements in a prospective study with controlled settings to evaluate diagnostic potential of TSAT as a marker for iron overload in HHA. Meanwhile, we suggest that, especially in situations where MRI is not available, patients who
have ferritin levels <500 ng/mL and TSAT <45% are unlikely to have iron overload.

We used a reference group of SCD and β-thalassemia patients. Percentage iron overload in our transfused SCD patients was comparable to published data.4 However, we did also find 2 patients with SCD (1 Hemoglobin SS [HbSS], 1 Hemoglobin SE [HbSE]) who were never transfused but did have LIC > 3 mg/g. This is interesting, as in general it is perceived that patients with SCD do not suffer from non-transfusion related iron overload.5

We included only patients who had MRI LIC data available. This creates a selection bias, but since we aimed to study the occurrence of iron overload and not its prevalence, the data can be considered representative. We did not correct for chelation therapy. Therefore, it is possible that the real prevalence of iron overload in HHA is even higher than described here, as effective chelation therapy reduces or even normalizes LIC levels. In this study, in order to completely eliminate the confounding effect of transfusions, we added a very strictly defined group of never-transfused patients. Even in this group there were patients with moderate to severe iron overload. This indicates that non-transfusion related iron overload, due to inappropriately increased dietary uptake, does occur in rare HHA.

In conclusion, this study demonstrates that iron overload is present in all forms of rare HHA, even in patients who were never transfused. The traditionally used cut-off of plasma ferritin >1000 ng/mL and even >800 ng/mL appears to be a poor predictor for liver iron overload. We suggest that all patients with rare HHA, possibly except those with ferritin levels below 500 ng/mL and TSAT below 45%, should be evaluated for iron overload with MRI.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest with the contents of this article.

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Performed data collection, analyzed results, made the Figures: S.S.
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Hemolysis and hemolysis-related complications in females vs. males with sickle cell disease

To the Editor:
Sickle cell disease (SCD) is an inherited red blood cell (RBC) disorder caused by homozygous or compound heterozygous mutations in the β-globin gene. The phenotype varies markedly and sex may contribute to this difference. Similar to the general population, females with SCD appear to have a survival advantage; the explanation for this difference is unclear. Increased hemolysis is associated with certain complications, such as leg ulcers, pulmonary hypertension, priapism, chronic kidney