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Case Report

Discrepancy between Serum Ferritin and Liver Iron Concentration in a Patient with Hereditary Hemochromatosis – The Value of T2* MRI

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Keywords
Hemochromatosis · Ferritin · Liver iron concentration · MRI

Abstract
Primary hemochromatosis is an inherited disorder, and the homeostatic iron regulator (*HFE*) gene C282Y mutation is a common cause of hemochromatosis in Europe. We are reporting a case of a 56-year-old female known to have hemochromatosis with the *HFE* gene C282Y mutation with a serum ferritin level of 482 µg/L who underwent heart and liver T2* MRI which showed no evidence of iron overload – neither in the heart nor in the liver. This indicates that there is a discrepancy between serum ferritin and liver iron concentration by MRI and the superiority of T2* MRI in diagnosis and follow-up of iron overload in patients with hereditary hemochromatosis.

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder considered as one of the most common inherited (genetic) disorders in the world. It is most commonly due to mutations in the HH gene (*HFE*). HH occurs when there is an increased intestinal iron absorption causing an increased total-body iron overload. HH has a low penetrance. Two common *HFE* mutations are observed C282Y (guanine to adenine change at nucleotide 845 in the *HFE* gene that causes a substitution of cysteine for tyrosine at amino acid 282) and

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H63D (cytosine to guanine change at nucleotide 187 in the *HFE* gene that causes a substitution of histidine to aspartic acid at amino acid 63) [1–4]. Iron overload can contribute to hemochromatosis but not all individuals with *HFE* mutations develop iron overload and clinical HH. There are other genetic and/or environmental factors, as well as other medical conditions, dietary iron intake, and blood loss (e.g., from physiologic bleeding such as menstruation or pathologic bleeding) which likely play a role in the manifestation of a clinically significant body iron burden. For those who are affected, classic HH generally does not become clinically manifest until later in adulthood when a significant total-body iron accumulation has occurred [5].

Case Presentation

A 56-year-old woman, with a known HH C282Y mutation and on phlebotomy when required, moved to Qatar 2 years ago. She was referred to the hematology clinic for further evaluation and to continue the medical care, as well as for an evaluation whether she still required further phlebotomy.

On her initial visit, she seemed to be in a fair general condition, and her clinical examination was not remarkable. Her complete blood count showed a white blood cell count of 6.8 × 10^3/μl (normal range 4–10), Hb of 14.5 g/dL (normal range 12–15), platelets of 208 × 10^3/μl (normal range 150–400), serum ferritin of 287 μg/L (normal range 18–340). An MRI of the liver was done which showed no evidence of iron overload: 0.9 mg/g dry tissue (normal range 0.17–1.8), 16 mmol/kg dry tissue (normal range 3–33). She was again evaluated 2 years later, when her serum ferritin level was found to be at 482 μg/L (normal range 18–340). Therefore it was decided to do a heart and liver MRI which showed <1.2 mg iron/g dry weight (no siderosis) in the heart and 3.4 mg iron/g dry weight (no siderosis) in the liver. There was no iron overload neither in the heart nor in the liver, which demonstrates the superiority of T2* MRI over serum ferritin.

Discussion

Chronic blood transfusion is the mainstay of care for individuals with β-thalassemia major. However, it causes an iron overload that requires monitoring and management by long-term iron chelation therapy to prevent endocrinopathies, liver dysfunction, and cardiomyopathies [6–11], which can be fatal. The hepatic R2 MRI method (FerriScan®) or T2* MRI has been validated as the gold standard for evaluating and monitoring liver iron concentration (LIC) that reflects the total body iron overload. Although adequate oral iron chelation therapy shows promising results for the treatment of transfusional as well as nontransfusional iron overload, compliance with medication remains an issue [12, 13]. Iron overload is an inevitable consequence of long-term transfusion therapy, for which iron chelation therapy is indicated and recommended. All patients who receive red blood cell transfusions and iron chelation therapy should be regularly monitored and given practical and educational support in order to improve compliance with therapy [14, 15]. In both nontransfusional and transfusion-dependent sickle cell disease, monitoring the liver iron status by measuring serum ferritin and LIC, using the FerriScan method, can diagnose early a hepatic iron overload. This helps to decide about starting and tailoring iron chelation accordingly to reduce the risk of developing hepatopathy in these patients [16].

β-thalassemia intermedia spans a wide spectrum of severity and carries a higher morbidity than previously recognized, including extramedullary hematopoiesis, leg ulcers,

gallstones, thrombosis, secondary heart failure, pulmonary hypertension, skeletal deformity, growth retardation, and endocrine abnormalities, such as diabetes mellitus, hypothyroidism, osteoporosis, and hypogonadism. A significant number of thalassemia intermedia patients have a high LIC, short stature, and endocrine disorders. Patients who require occasional transfusions have a higher liver iron overload and higher hepatic dysfunction. Females appear to attain a better final adult height and have higher IGF1-SDS versus males [17].

HH is an autosomal recessive disorder characterized by an excessive intestinal absorption of dietary iron, causing an iron overload in different organs, especially the liver. Hemochromatosis may remain unrecognized until later in life. Patients are usually asymptomatic, but they may present with a variety of signs and symptoms. These include hyperpigmented skin, hepatomegaly, arthralgia, diabetes mellitus, and/or heart failure/arrhythmia. For the risk of HH-related morbidity in HFE mutation carriers [18], serum ferritin levels are not an accurate measure of total body iron stores in HH. The use of T2* MRI should be encouraged in patients with HH for a better evaluation of iron overload and the avoidance of complications, since the serum ferritin level can be misleading in these conditions [18].

Conclusion

HH is known to cause an iron overload which is generally followed up by serum ferritin measurements to decide about phlebotomy; however, in the era of T2* MRI and its reported superiority, T2* MRI should be utilized for the diagnosis and follow-up of patients with an iron overload whenever it is available.

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Statement of Ethics

This case was approved by the Hamad Medical Corporation's Medical Research Center. The patient consented to the publication of his case.

Disclosure Statement

The authors have no conflicts of interest.

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Author Contributions

Both authors contributed equally to writing and editing.

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