Clinica Chimica Acta 412 (2011) 1485–1492

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Hereditary hemochromatosis: Laboratory evaluation

Thomas P. Moyer [a,*], W. Edward Highsmith [b], Thomas C. Smyrk [c], John B. Gross Jr. [d]

[a] Department of Laboratory Medicine & Pathology, Division of Clinical Biochemistry & Immunology, Mayo Clinic, Rochester, MN 55905, United States
[b] Department of Laboratory Medicine & Pathology, Division of Laboratory Genetics, Mayo Clinic, Rochester, MN 55905, United States
[c] Department of Laboratory Medicine & Pathology, Division of Anatomic Pathology, Mayo Clinic, Rochester, MN 55905, United States
[d] Department of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, United States

ARTICLE INFO

Article history:
Received 4 March 2011
Received in revised form 6 April 2011
Accepted 8 April 2011
Available online 13 April 2011

Keywords:
Hereditary hemochromatosis
Iron overload
HFE gene
Hepatic iron

ABSTRACT

The condition of hereditary hemochromatosis (HH) is caused by gene-dependent protein abnormalities involved in iron absorption, storage, or modulation of iron; these abnormalities result in iron overload. The clinical laboratory plays a significant role in case finding, diagnostic validation, and monitoring HH therapy. Elevated serum iron, transferrin saturation, and ferritin suggest HH, but results can also indicate other forms of hepatocyte injury such as alcoholic or viral hepatitis, or other inflammatory disorders involving the liver. In the context of elevated serum iron, transferrin saturation, and ferritin, and after ruling out secondary causes of iron overload, *HFE* gene evaluation is the preferred test to confirm the diagnosis of HH. However, 5% to 15% of patients with phenotypic HH do not have *HFE* gene mutations. In these cases, MRI evaluation or liver biopsy with iron quantification is indicated. The clinical role of hepcidin, the iron modulating protein, is undetermined at this time. Because hepcidin also plays a key role in antimicrobial and inflammatory activities, interpretation of hepcidin serum or urine concentration will require thorough understanding of its complex role in iron regulation.

Contents

1. Overview

Diseases affecting the liver have profound consequences requiring early intervention. One common finding in liver disease is hemosiderosis, the condition of excessive iron accumulation, often described as iron overload. Liver is the first organ affected in iron-overload diseases. Iron catalyzes the formation of oxygen radicals that promote cell injury and activation of hepatic stellate cells, leading to fibrosis and, ultimately, cirrhosis. Increases in iron first appear in Kupffer cells and hepatocytes. This finding is commonly associated with sideroblastic anemia, excessive iron consumption, viral infection, chronic alcohol ingestion, or repeated transfusions. Persistent hemosiderosis with iron accumulation in biliary hepatocytes is typical of hereditary hemochromatosis (HH).

Hemochromatosis was first described in 1865 by Trousseau and later characterized and named by von Recklinghausen in 1889. The disease is characterized by an accelerated rate of intestinal iron

* Corresponding author.
E-mail addresses: moyer.thomas@mayo.edu (T.P. Moyer), highsmith.w@mayo.edu (W.E. Highsmith), smyrk.thomas@mayo.edu (T.C. Smyrk), gross.john@mayo.edu (J.B. Gross).

0009-8981/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.cca.2011.04.007

absorption and progressive iron deposition in various tissues that is typically expressed in the third to fifth decades of life; the most severe variants of the disease may be expressed in children. The most common presentations are hepatic cirrhosis and arthritis, but hypopituitarism, cardiomyopathy, diabetes, or hyperpigmentation may be seen. Because of the severe sequelae of this disease if left untreated, and recognizing that treatment is relatively simple, early diagnosis is important before signs or symptoms appear.

In a review, Franchini and Veneri [1] defined several variants of hereditary hemochromatosis (HH).

- Hereditary hematochromatosis type I (OMIM 235200) is the classical *HFE*-related disorder associated with mutations in the *HFE* gene expressed as HFE protein variants C282Y and H63D. This is an autosomal recessive disease with estimated prevalence in the population of 2 in 1000 in Caucasians, with lower incidence in other races. This gene is at chromosome location 6p21.3; the majority of hemochromatosis patients have this type.
- Hereditary hematochromatosis type IIa (OMIM 602390), also called juvenile hemochromatosis (JH), is a rare, more severe form of the disease that occurs before age 30, caused by mutations in the hemojuvelin gene (*HJV*) located on chromosome 1q21.
- Hereditary hematochromatosis type IIb (OMIM 606464) is even more severe than type IIa, caused by mutations in the *HAMP* gene located on chromosome 19q13 coding for the protein/hormone hepcidin.
- Hereditary hematochromatosis type 3 (OMIM 606250) is an autosomal recessive disease caused by mutations in the transferrin receptor 2 gene (*TfR2*) located on chromosome 7q22 coding for the protein transferrin receptor 2.
- Hereditary hematochromatosis type 4 (OMIM 606069) is an autosomal dominant disease caused by mutations in *SLC40A1* gene coding for the hepcidin-resistant form (C326S) of the metal transport protein ferroportin.
- Hyperferritinemia-cataract syndrome is a rare autosomal dominant disease caused by mutations in the ferritin L-subunit gene located on chromosome 19q13 coding for the protein iron-responsive element (IRE) that facilitates high serum ferritin without iron overload.

Serum iron concentration and transferrin saturation are commonly used clinical tests to screen for HH. If the serum transferrin saturation is elevated, serum ferritin evaluation is recommended. Elevated serum iron, transferrin saturation, and ferritin, indicating increased iron stores, are commonly associated with HH, but also with other forms of hepatocyte injury such as alcoholic or viral hepatitis, or systemic inflammatory disorders. *HFE* gene evaluation is the next test to be considered in the diagnostic algorithm for HH, or for predictive testing of individuals who have a family history of HH [2, 3]. If *HFE* gene evaluation is negative, and no other obvious cause for increased iron stores is evident, liver biopsy histologic evaluation and iron quantification may be performed. Iron accumulation in biliary hepatocytes and increased iron concentration indicate HH, which is responsive to regular phlebotomy therapy (Fig. 1).

2. Normal iron metabolism

A typical human adult absorbs 1–2 mg of iron per day from the diet. Iron is taken up from the lumen of the intestine by the duodenal villus cell through a process involving Ferrireductase (DcytB) and Divalent Metal Ion Transporter (DMT1, SLC11A2), both membrane-bound proteins. Apical membrane-bound DcytB converts absorbed Fe^{+3} to Fe^{+2}. Apical membrane-bound DMT1 transports Fe^{+2} from the lumen of the intestine into the villus cell. Cellular Fe^{+2} is subsequently transported from the cell into the blood via a basal membrane-bound ion transporter, ferroportin (SLCA40A1). In the blood, Fe^{+2} is converted to Fe^{+3} by the villus cell basal membrane-bound protein, hephaestin. In the Fe^{+3} state, iron binds avidly to apotransferrin to form transferrin, the primary form of protein bound iron circulating in the blood serum [4, 5] (Fig. 2).

Downstream from the duodenal villus cell, the duodenal crypt cell re-absorbs iron through a process involving a complex comprised of circulating beta-2-microglobulin with crypt cell membrane-bound

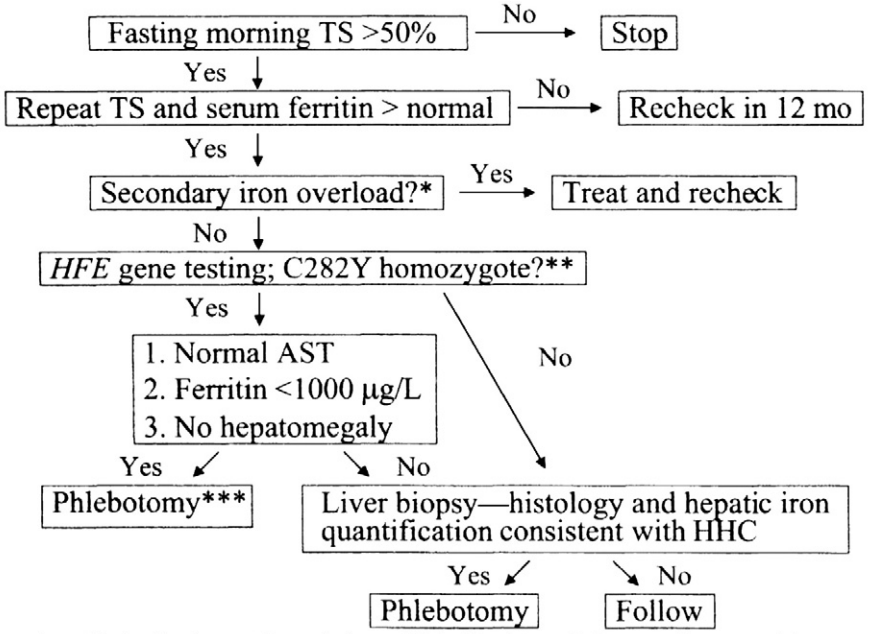

Fig. 1. Diagnostic algorithm for hereditary hemochromatosis by DJ Brandhagen (1999).
Source: (From Brandhagen DJ, Fairbanks VF, Batts K, Thibodeau SN. Update on hereditary hemochromatosis and the HFE gene. Mayo Clin Proc 1999;74(9):917–21. Used with permission.)