Hemochromatoses
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Hemochromatoses definition. In the field of chronic iron overload diseases, hemochromatoses (H) (Box 1) are genetic diseases where iron overload is due to hepcidin deficiency and, much more rarely, to hepcidin resistance. These disorders are related to mutations of HFE or non-HFE genes that are involved in the control of hepcidin expression or bioactivity that tunes systemic iron homeostasis (Box 2) (1).

Pathophysiology. (Box 3) Mutations of proteins, including HFE, transferrin receptor 2 (TFR2) and hemojuvelin (HJV), that are located at the cell membrane of hepatocytes, are responsible for defective iron status sensing. These mutations lead to an abnormally low transduction signal for the synthesis of hepcidin, despite increasing iron levels. The reduced circulating hepcidin (follow red dashes lines) means that the iron transport function of the ferroportin protein (normally under hepcidin control) is not appropriately reduced, especially in enterocytes and macrophages. As a result, plasma iron and transferrin saturation increase. In turn, non-transferrin bound iron (NTBI) forms appear and “rushes” into the hepatocytes causing cellular iron excess. Whenever transferrin saturation exceeds 75%, a component of this plasma NTBI (reactive plasma iron) can exert cellular and tissue toxicity (Box 4). When mutations of the ferroportin gene (SLC40A1) affect its normal interaction with hepcidin (Box 3) (follow purple items), there is hepcidin “resistance”, the metabolic consequences of which are similar to those of hepcidin deficiency.

Diagnostic aspects. (Box 5) H can now be diagnosed non-invasively (without liver biopsy). The diagnostic approach combines: a) Clinical examination, b) Laboratory data, namely increased plasma transferrin saturation and ferritin, followed by genetic testing which, in case of non-HFE H, requires expert centers, and c) “Iron-MRI”. MRI, whenever feasible, is mostly indicated if there are cofactors likely to increase serum ferritin, so that it no longer purely reflects body iron stores. MRI permits visualization and quantification of hepatic iron overload, and, by showing the absence of iron overload in the spleen, strongly supports the mechanism of hepcidin deficiency (or resistance). For liver complications, the key point is to establish whether or not there is cirrhosis (by transient elastography and/or liver biopsy), especially when serum ferritin has chronically been over 1000 ng/mL and/or transaminases are raised. Detecting cirrhosis is essential since it will lead to screening for hepatocellular carcinoma by serial ultrasound examination (1).

Main differential diagnoses (Box 6) There are two in particular: a) Non-genetic iron overload, mainly due to transfusions, excessive parenteral iron supplementation or ineffective erythropoiesis, and b) Genetic non-H iron overload. This latter group includes in particular: i) Ferroportin disease (2) in which, due to an impaired iron export function of ferroportin, iron is trapped inside cells, especially splenic macrophages. Therefore, iron overload occurs through cellular iron retention, explaining why this type of iron overload is not accompanied by a raised plasma iron or transferrin saturation, and therefore why plasma NTBI is not present. Thus, there is rather mild disease; ii) Hereditary aceruloplasminemia in which the pathophysiological understanding of iron excess needs to be further clarified (3). Most non-H iron overload entities are associated with anemia or a trend to anemia (4) in marked contrast with H where there is no anemia.

Therapeutic aspects (limited to iron overload therapy) (Box 7). Phlebotomy remains the mainstay for removing established iron excess. The key target is to reach and maintain serum ferritin around 50 ng/mL (5). Maintaining transferrin saturation around 50% may also be worthy of consideration (6). Innovative approaches (7), like parenteral exogenous hepcidin supplementation, parenteral endogenous stimulation of hepcidin synthesis, or inhibition of enterocyte iron absorption using an oral ferroportin antagonist, have experimentally achieved their proofs of concept. Many advances,
however, are still needed before these approaches, aiming at safely restoring normal systemic iron homeostasis, become clinically applicable as an adjunct to phlebotomies during the induction phase and/or replace phlebotomy during maintenance therapy. 

References

**Hemochromatosis**

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**Definition**

Iron overload of genetic origin and related to relative hepcidin deficiency with regard to iron status or, rarely, to hepcidin resistance.

**Pathophysiology: from gene to hepcidin deficiency/resistance syndromes**

- HFE gene
- HJV (hemojuvelin)
- HAMP (hepcidin)
- TFR2 (transferrin receptor 2)
- SLC40A1 (ferroportin)

**HFE Clinical Findings**

- Variable penetrance
  - Adult (> 30 yrs)
  - Caucasian
  - Fatigue/impotence
  - Arthropathy
  - Bronze skin
  - Liver disease (see text)
  - Diabetes mellitus

**Laboratory Data**

- Transferrin saturation
- Serum ferritin

**Non-HFE Clinical Findings**

- Rare but not limited to Caucasians
- Younger (< 30 yrs)
- Enhanced classical HFE signs
  - Cirrhosis (see text)
  - Cardiac failure
  - Endocrine dysfunction
  - Massive iron overload

**Imaging Data (MRI-7T)**

- Hemochromatosis
- Non-HFE

**Genetic Testing**

- by expert center

**Hemochromatosis: differential diagnosis**

- Iron overload with high transferrin saturation
- Iron overload with normal or low transferrin saturation
- Iron overload with high transferrin saturation

**Context of chronic anemia**

- Transfusional iron overload
- Excessive parenteral iron supplementation
- Dyserythropoiesis

**Hemochromatosis: iron overload management**

- Iron depletion therapy
  - Phlebotomy
    - Mainstay of treatment
    - Targets: Serum ferritin around 50 ng/ml, (key target)
    - Transferrin saturation around 50% (see text)
- Oral iron chelation
  - Rarely used
  - Off-label drug

**Disease prevention**

- Family screening
- Increased awareness in medical profession and general population
- Population screening (?)

**Treatments in development**

- Hepcidin supplementation
- Intestinal inhibition of ferroportin
- Iron transport activity