

Epidemiology and Disease Pathophysiology: Hereditary Haemochromatosis

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The world of genetic iron-related diseases is rapidly and fundamentally changing. Through genetic analysis, haemochromatosis (HC) has been broken down into five main entities:

- Type 1 – HFE-HC, caused by HFE gene mutations and exclusively seen in Caucasian populations
- Type 2 – juvenile HC, resulting from haemojuvelin (2A) or hepcidin (2B) mutations
- Type 3 – TfR2 (transferrin receptor 2) HC, due to TfR2 gene mutations
- Type 4 – ferroportin disease, caused by ferroportin (SLC40A1) gene mutations; type 4 may be subtype “A” (low transferrin saturation and macrophage iron deposition) or “B” (high transferrin saturation and hepatocytic iron deposition)
- Aceruloplasminaemia, caused by ceruloplasmin gene mutation and resulting in lower than normal serum ceruloplasmin and iron deposits in the liver and brain

Other types of non-HFE haemochromatosis include atransferrinemia caused by mutation in the transferrin gene, DMT1-mutation related iron overload, and GLRX5-mutation related iron overload.

Normally, iron in the plasma is carried via transferrin to the body's cells; this distribution is mediated by the transferrin receptors. Some iron (about 70%) is used in erythroid cells for the transport of oxygen throughout the body; iron may be released into the plasma by macrophages by means of ferroportin 1. Together, these two processes create a closed circle whereby the body can recycle iron. In HC types 1, 2 and 3, however, hepcidin deficiency increases iron delivery from enterocytes and macrophages into the bloodstream; the presence of non-transferrin-bound iron creates conditions leading to plasma and hepatocytic iron overload. In ferroportin disease (subtype A), mutations in the ferroportin protein make it less effective in exporting iron from the macrophages into the blood, thereby leading to iron overload.

Numerous clinical symptoms, including asthaenia, arthropathy, osteopaenia, skin pigmentation changes, impotence, diabetes, liver signs such as hepatomegaly, and cardiac symptoms, are associated with iron overload. Biochemically, hyperferritinaemia is a key parameter reflecting

increased iron stores (with a level >300 mg/L in men with HC and >200 mg/L in women with HC) provided that confounding factors like alcoholism, polymetabolic syndrome, inflammation, and hepatitis have been ruled out. Plasma transferrin saturation (TS) values are pivotal for the etiologic diagnosis of HC; TS is highly elevated in types 1, 2, 3, and 4(B) HC, whereas it is normal or low in cases of ferroportin disease type A and in aceruloplasminaemia.

Hepatic and splenic MRI evaluation of iron content is a valuable, non invasive way to quantify iron overload and diagnose HC. In fact, the accuracy and availability of MRI have made the need for liver biopsy rare in the diagnosis of HC.

Venesection therapy (phlebotomies) remains the mainstay of treatment for HC forms related to hepcidin deficiency. The improved understanding of the pathophysiologic mechanisms underlying these diseases has paved the road for innovative therapeutic approaches. Hepcidin supplementation has become a major therapeutic challenge for HC. Chelation therapy with deferasirox is under exploration in type-1 HC. It may be of special interest in ferroportin disease type A and mostly in aceruloplasminaemia due to the risk of anaemia.

Suggested Readings

Brissot P, de Bels F. Current approaches to the management of hemochromatosis. *Hematology*. 2006;36-41.

Camaschella C, Campanella A, De Falco L, et al. The human counterpart of zebrafish shiraz shows sideroblastic-like microcytic anemia and iron overload. *Blood*. 2007;110:1353-1358.

Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β -thalassemia. *Blood*. 2006;107:3455-3462.

De Domenico I, Ward DM, di Patti MC, et al. Ferroxidase activity is required for the stability of cell surface ferroportin in cells expressing GPI-ceruloplasmin. *EMBO J*. 2007;26:2823-2831.

Gandon Y, Olivié D, Guyader D, et al. Non-invasive assessment of hepatic iron stores by MRI. *Lancet*. 2004;363:357-362.

Ganz T. Molecular control of iron transport. *J Am Soc Nephrol*. 2007;18:394-400.

Haute Autorité de Santé (HAS). French recommendations for management of HFE hemochromatosis. 2005. Available at: http://www.has-sante.fr/portail/display.jsp?id=c_432802. Accessed October 4, 2007.

Loréal O, Haziza-Pigeon C, Troadec M, et al. Hepsidin in iron metabolism. *Curr Protein Pept Sci*. 2005;6:279-291.

Mims MP, Guan Y, Pospisilova D, et al. Identification of a human mutation of DMT1 in a patient with microcytic anemia and iron overload. *Blood*. 2005;105:1337-1342.

Papanikolaou G, Samuels ME, Ludwig EH, et al. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. *Nat Genet*. 2004;36:77-82.

Pietrangelo A. The ferroportin disease. *Blood Cells Mol Dis*. 2004;32:131-138.

Roetto A, Papanikolaou G, Politou M, et al. Mutant antimicrobial peptide hepcidin is associated with severe juvenile hemochromatosis. *Nat Genet*. 2003;33:21-22.