

Hereditary hemochromatosis

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Hereditary hemochromatosis (HH) is the most commonly identified autosomal recessive genetic disorder in the white population, characterized by increased intestinal iron absorption and secondary abnormal accumulation in parenchymal organs, not infrequently accompanied by functional impairment.¹ This entity is associated with mutations of the HFE gene (located on the short arm of chromosome 6 at location 6p22.2; closely linked to the HLA-A3 locus), which encodes the HFE protein, a membrane protein thought to regulate iron absorption by affecting the interaction between transferrin receptor and transferrin. One of

these mutations results in a substitution of tyrosine for cysteine at the amino acid 282 position (C282Y).^{2,3} Subsequently two additional mutations have been noted, aspartate for histidine (H63D), and cysteine for serine (S65C), however the most common form of HFE-related HH is associated with the C282Y homozygous mutation.⁴ The presence of this mutation varies between 69% to 100% in series from USA, France, Italy, Australia, Germany.⁵⁻⁹ Other HFE defects in addition to homozygosity for C282Y, are found: homozygosity for the H63D mutation, heterozygosity for the C282Y or H63D mutation, or compound

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heterozygosity.¹⁰ Less commonly, the hemojuvelin, hepcidin, ferroportin, or ceruloplasmin encoding genes may also be associated with HH.

There is a substantial controversy on the likelihood of homozygous patients for C282Y developing clinically apparent disease. In a USA screening study involving 41,000 adults, 152 individuals were positive for C282Y homozygosity, but only one fit the criteria for the diagnosis of HH (penetrance < 1%).¹¹ In contrast, the Australian series of 31,192 subjects of northern European ancestry found 203 C282Y homozygous. These individuals were followed for 12 years, with 28% of men and 1.2% of women presenting with clinical HH.¹²

Once thought to be a rare disease, HH was initially considered when the patient presented an unusual manifestation such as "bronze diabetes". Indeed the first case description by Armand Trousseau, in 1865, was of a diabetic patient with hepatic cirrhosis and bronzed skin. The name hemochromatosis was applied in subsequent 1890 report by Daniel von Recklinghausen. Recklinghausen suggested the association between tissue iron storage and the resultant condition. The image above shows well the brown discoloration of the liver and also the pancreas, the body of which is almost mahogany. The inherited nature of the disease was first explained by J.H. Sheldon in his textbook *Haemochromatosis*. He also suggested an abnormality of iron metabolism as the basis for the disease.

With genetic studies, families have been accurately studied showing that transferrin saturation values greater than 60% in men and greater than 50% in women (in the absence of hepatopathy of any etiology) indicates the presence of abnormality in iron metabolism with 95% accuracy. In the USA and Europe the frequency of HFE mutations among Caucasian is 10% for heterozygous and 5 per 1000 (0.5%) for homozygous.¹³

Body iron stores inversely correlate with the normal intestinal absorption of heme and non-heme iron. In HH this regulation is lost and iron overload ensues since there is no mechanism for excess excretion. Clinical symptoms appear when greater than 20g of iron is accumulated in the body, typically occurring after the age of 40 in men and, when menstruation occurs, 50 in women. Differing from acquired (secondary)

hemochromatosis, HH iron is initially stored in parenchymal cells and later in the reticuloendothelial system cells.

The clinical picture reflects the involvement of liver, skin, pancreas, joints, and heart, with impotence in males.¹⁴ Liver function abnormalities, weakness and fatigue, and skin hyperpigmentation were present in more than 70% of cases in the series by Niederau et al¹⁴.

Liver involvement manifests as hepatomegaly, increasing fibrosis and eventual cirrhosis, potentially reversible in early stages. Although infection with hepatitis-C virus may potentiate fibrosis, the major risk co-factor for the development of liver disease is excess alcohol intake. The deposition of iron alone in hepatocytes is not inflammatory and hepatic fibrosis may ensue with low or normal serum aminotransferase determinations.^{15,16} However in almost 50% of patients with HH, another cause of liver disease is present that is more likely responsible for hepatic liver enzyme elevations. Hepatocellular carcinoma is the most serious complication of the hepatic iron overload. The magnitude of the risk varies between 20- to 200-fold.^{17,18}

Pancreatic deposition of iron occurs in beta cells and diabetes is clinically demonstrable in 50% of symptomatic patients. Although insulin and C-peptide secretion are reduced, the alpha cell function remains intact, and glucagon values are similar to those in type-1 diabetes.¹⁹

HH can lead to dilated cardiomyopathy, heart failure and conduction disturbances, such as sick sinus syndrome.^{20,21}

Arthritis associated with HH clinically resembles rheumatoid arthritis with predominant involvement of metacarpophalangeal joints. The iron deposition within the joints triggers an inflammatory process that is often complicated by calcium pyrophosphate deposition ("pseudogout") and subsequent chondrocalcinosis and chronic arthropathy.²²⁻²⁴

Secondary hypogonadism, responsible for impotence and decreased libido in men, is the result of iron deposition in the anterior pituitary, which results in low levels of trophic hormones (e.g., follicle stimulating hormone) and therefore testosterone. Amenorrhea rarely occurs in women and is much less common than hypogonadism in men.^{25,26}

The diagnostic workup of HH includes determination of iron overload (increased body

iron burden), family history of this disorder and genetic studies. In addition to serum iron assay, liver biopsy and magnetic resonance imaging studies are usually employed. However liver biopsy is often not performed for patients with HH when the diagnosis is clearly established based upon genetic testing, including findings of C282Y/C282Y, heterozygous C282Y, and C282Y/H63D genotypes. The findings of H63D homozygosity or heterozygosity is of uncertain significance since most will not present iron overload.^{27,28}

Keywords: hemochromatosis, Iron Overload, Liver Diseases, Pancreatic Disease.

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