hematology

Hemochromatosis

HEREDITARY HEMOCHROMATOSIS (HH) is an autosomal recessive disorder with increased iron absorption, which sometimes causes excessive iron stores

Hemochromatosis overview

Hereditary hemochromatosis (HH) is an autosomal recessive disorder with increased iron absorption, which sometimes causes excessive iron stores. HH is caused by variants in the HFE gene, typically homozygous C282Y/C282Y and less commonly compound heterozygous C282Y/H63D.

HH is a genetic disease caused by abnormal levels of iron. It is regarded as more common than most people think and as underdiagnosed. It can cause liver disease, arthritis, pituitary disease and abnormal skin colour.

HH is a term generally used to define a group of autosomal recessive genetic disorders characterised by iron accumulation in parenchymal organs, primarily the liver, which can potentially result in impaired organ structure and function. In recent years, hepcidin has been identified as the key hormone that controls the saturation of plasma transferrin with iron (transferrin saturation). Hepcidin deficiency causes increased transferrin saturation, which is the unifying feature and principal biochemical finding of all forms of HH.

Genes that stimulate hepcidin production such as HFE, HJV and TFR2 are therefore associated with hemochromatosis.

Adult males have approximately 1 g of storage iron (mostly in liver, spleen, and bone marrow). Adult females often have less storage iron, depending upon the menses, pregnancies, deliveries, and iron intake; some may have no iron stores.

Normal iron stores

The normal iron content of the body is 3 to 4 grams, distributed as follows:

- Haemoglobin in circulating red blood cells (RBCs) – Approximately 2.5 grams
- Iron-containing proteins other than haemoglobin (eg, myoglobin, cytochromes, catalase) – 400 mg
- ron bound to circulating transferrin – 3 to 7 mg
- Storage iron in the form of ferritin or hemosiderin (typically in bone marrow macrophages)

Less common forms of HH include other HFE variants and pathogenic variants in other iron regulatory genes:

- Ferroportin
- Hemojuvelin
- Hepcidin
- Ceruloplasmin
- Transferrin receptor 2

Individuals with HH can absorb as much as 2 to 4 mg of dietary iron per day (twice the rate of individuals without HH). This increased absorption can result in as much as an additional 3 mg per day in excess of needs, which are typically 1 to 2 mg per day.

Over time, iron accumulation can occur at a rate of approximately 1 gram per year (10 grams per decade). This explains the typical age of presentation (fourth to fifth decades in males; later in females, due to iron loss with menstruation and/or pregnancy).

Individuals with a family history of HH should have HFE testing (or testing for other familial gene variants) to identify HH if present and prevent permanent end-organ damage. In the Hemochromatosis and Iron Overload Screening (HEIRS) study, self-reported information about the family history had a sensitivity of 81 percent and a specificity of 97 percent for an accurate report, supporting the use of family history as a screening tool. Individuals who are homozygous for HFE C282Y or compound heterozygous (C282Y/H63D) should have iron

studies and liver function tests.

The ideal age to perform genetic testing and/or liver iron assessment has not been determined. Deferring screening until adulthood is reasonable to facilitate informed consent for testing and given that clinically significant iron loading usually is not present in the first couple decades of life.

The appropriate screening tests include HFE genetic testing and iron studies. These can be done sequentially (HFE testing followed by iron studies only in those with the HH genotype); it may be cost effective to order the testing simultaneously. Screening relatives of an individual with HH and interpretation of the results are discussed separately.

Diabetes mellitus and hemochromatosis

Pancreatic iron overload can lead to type 2 diabetes mellitus (DM). Iron deposition appears relatively selective for pancreatic beta cells (the insulin- and C-peptide-secreting cells); pancreatic alpha cell function (glucagon secretion) seems relatively intact. Type 2 DM in combination with skin discoloration led to the past designation of individuals with HH as having "bronze diabetes" .

DM has been reported in as many as 50 percent of patients with HH who present with symptoms. However, the baseline prevalence of type 2 DM is high in the general population, and a study that screened for HH in a population of 220 individuals with DM did not find an increased incidence of HH compared with 220 age-matched, sex-matched controls [64]gous (C282Y/H63D) should have iron studies and liver function tests.

Arthropathy

HH can be associated with an arthropathy that causes symptoms of arthritis, arthralgias, and radiologic findings indistinguishable from calcium pyrophosphate crystal deposition disease. Joints in the hands are often affected. The mechanism remains unclear, as does the predilection for the second and third metacarpophalangeal joints.

In contrast to many other manifestations of HH, reports from the 1990s suggested that iron removal was less effective for reversing the disease process in HH-associated arthropathy. However, these findings likely reflected relatively late intervention in the disease process, and earlier intervention may be more effective.

Gene testing

Since 1996, HFE genotyping was implemented in diagnostic algorithms for suspected HH, allowing its early diagnosis and prevention. However, the penetrance of disease in p.C282Y homozygotes is incomplete. Hence, homozygosity for p.C282Y is not sufficient to diagnose HH. Neither is p.C282Y homozygosity required for diagnosis as other rare forms of HH exist, generally referred to as non-HFE-related HH.

Example of results from a patient:

HEREDITARY HEMOCHROMATOSIS DNA MUT

RESULT: POSITIVE FOR ONE HFE GENE PATHOGENIC VARIANT: C282Y

(HETEROZYGOTE)

Interpretation: One copy of the C282Y pathogenic variant in the HFE gene was detected. This patient is negative for the H63D pathogenic variant. Individuals with this genotype may have elevated serum transferrin iron saturation levels. This result reduces the likelihood of hereditary hemochromatosis (HH). However, it does not rule out the presence of other pathogenic variants within the HFE gene or a diagnosis of HH. The risk of this individual to carry an HFE pathogenic variant other than those tested in this assay depends greatly on family and clinical history as well as ethnicity. This assay does not test for other primary or secondary iron overload disorders. Consider genetic counselling and DNA testing for at-risk family members.

References

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Algorithm for hemochromatosis diagnosis