COLLEGE of AMERICAN PATHOLOGISTS

Genetic Hemachromatosis

SYNOPSIS AND RELEVANCE

Genetic hemochromatosis is a common autosomal recessive hereditary disorder of iron metabolism that if left untreated can lead to severe complications from iron toxicity, including hepatic failure and malignancy. The diagnosis of the most common form of this disease is genotyping of the *HFE* hemochromatosis gene in suspected patients based on either family history or abnormal laboratory results (eg, elevated iron saturation). Selection of appropriate criteria for HFE genetic testing and accurate interpretation of test results to inform treatment and management are important considerations to optimize care.

INSIGHTS

1. HFE gene testing is indicated for patients with unexplained elevated transferrin saturation (greater than [>] 45%) levels.[1]
2. HFE testing for genetic hemochromatosis is generally not indicated for screening or in patients with normal iron studies unless there is a family history.
3. Hyperferritinemia alone without elevated transferrin saturation should not be used as an indication for HFE gene testing.
4. Therapeutic phlebotomy should be limited to only HFE gene mutations associated with iron toxicity complications, eg, homozygous p.C282Y/p.C282Y and compound heterozygous (p.C282Y/p.H63D, p.C282Y/p.S65C) genotypes.
5. HFE genetic testing should only be performed once unless there is some concern about reliability of prior test results.

BACKGROUND

Serum ferritin, iron, iron binding capacity, and transferrin saturation are common laboratory studies used to evaluate iron status. Transferrin saturation normally ranges between 15-30%. Approximately 2% of the adult US population have highly elevated transferrin saturation levels (> 45%) which is associated with higher risk for all-cause mortality.[2]

High transferrin saturation is most often associated with secondary causes such as chronic blood transfusions, hemolytic disease, poisoning, or chronic liver disease (eg, viral hepatitis, alcohol, porphyria). Less often, elevated transferrin saturation is a sign of genetic hemochromatosis, an autosomal recessive disorder of iron metabolism. This is one of the most common hereditary disorders which affects about 1 of 200 individuals of northern European descent.

While serum ferritin is also elevated in patients with hemochromatosis, this is usually due to secondary causes such as inflammation or tissue injury and does not accurately reflect iron status, especially if transferrin saturation is not likewise elevated.10 Furthermore, abnormal transferrin saturation levels typically appear sooner than elevated serum ferritin in patients with early, asymptomatic hemochromatosis. Therefore, HFE gene testing is indicated when transferrin saturation is elevated even when serum ferritin is normal. Transferrin saturation (> 45%) is preferred over hyperferritinemia as an indicator for genetic testing.

Two *HFE* gene pathogenic variants, p.C282Y (c.845G>A) and p.H63D (c.187C>G), are the most common causes of genetic hemochromatosis. While more than 20 other pathogenic variants in the *HFE* gene have been identified, about 85% of genetic hemochromatosis cases are associated with homozygous p.C282Y, while most of the remaining are compound heterozygous, p.C282Y/p.H63D or rarely p.C282Y/p.S65C (c.193A>T). These genotypes are associated with toxic injury to the liver and other organs that can be prevented by removing iron by regular therapeutic phlebotomies.[3-5] Other mutations (eg, heterozygous C282Y) are not typically associated with iron toxicity even when iron saturation is elevated and therefore do not require intervention (eg, therapeutic phlebotomy), other than possibly screening family members for HFE gene mutations.[5]

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