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Diagnosis and Management of Hereditary Hemochromatosis

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Hereditary hemochromatosis (HH) is a heterogeneous genetic disorder that results in unregulated and excessive intestinal iron absorption leading to overabundance of iron deposition in tissue. HH is most common in people of northern European ancestry, for whom the prevalence is 1 case per 300 people.[1-3]

Pathogenesis

Dietary iron is absorbed in the duodenum. Ferroportin, a transport protein on duodenal epithelial cells, hepatocytes, and macrophages, transfers iron from the duodenum and proximal jejunum into the circulation. Iron circulates bound to transferrin and is deposited as ferritin in tissues.[1] Hepcidin, a protein produced by hepatocytes in response to circulating iron, binds to ferroportin leading to its degradation, which reduces iron release from enterocytes to the circulation. Molecular defects that cause hepcidin deficiency, such as those in the *HFE* gene (homeostatic iron regulator gene), result in uncontrolled iron absorption and iron accumulation in tissues.[4]

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Supplemental content

HH is caused by variants in at least 5 genes that reduce production of hepcidin or, less commonly, cause ferroportin resistance to hepcidin (eTable in the Supplement). HH is classified into 4 types based on the molecular defect.[5] Approximately 95% of cases involve *HFE* and the C282Y variant. Homozygous C282Y accounts for 90% of HH cases, with 5% attributed to C282Y/H63D heterozygotes.[2] However, homozygous C282Y exhibits incomplete (50%-90%) penetrance.[6] Only approximately 5% of people with the C282Y/H63D genotype develop iron overload.[6] Factors that modify the degree of iron overload–related clinical manifestations include age, sex, ancestry, comorbidity, and environment.

Clinical and Laboratory Characteristics

Clinical presentation of HH is variable, and approximately 90% of patients are asymptomatic.[3] HH should be suspected in patients with fatigue, arthralgias, or any elevation in transaminase levels and in patients with hepatomegaly or cardiomyopathy of unknown origin. HH should be evaluated in first-degree relatives of patients with HH by measuring concurrent serum transferrin saturation level, ferritin level, and *HFE* genotype (**Figure**). Clinical penetrance of HH is higher and occurs earlier in men than in women, possibly because women have iron loss during menstruation.[1]

Approximately 25% of people with HH have liver involvement. Those with serum ferritin level greater than 1000 ng/mL are at highest risk for advanced fibrosis.[1] Men with untreated HH have approximately a 9% lifetime risk of developing cirrhosis.[2] Patients with cirrhosis have an increased risk of hepatocellular carcinoma (HCC).[1] Approximately 15% of people with HH have cardiac involvement, although only approximately 0.9% to 3% of people with HH develop cardiomyopathy.[2] Cardiomyopathy can be both restrictive and dilated, with associated risk of arrhythmias and heart failure.[1] Arthralgias are common in patients with early disease and usually involve the second or third metacarpophalangeal joints.[3] Endocrine abnormalities include diabetes or hypogonadotropic hypogonadism due to iron deposition in the pancreas and pituitary gland, respectively.[1] Approximately 70% of people with advanced HH develop skin hyperpigmentation.[1]

Initial evaluation for HH includes measuring serum transferrin saturation (TSAT) levels. Approximately 98% of patients with type I HH have a TSAT level greater than or equal to 45% (reference range, 20%-45%).[1] However, young patients and those with non–type 1 HH may have TSAT levels less than 45%.[1] Ferritin greater than 300 ng/mL in men and greater than 200 ng/mL in women suggests iron overload, although in untreated HH, ferritin is often greater than 1000 ng/mL. Ferritin is an acute phase reactant. Inflammatory states, including other liver diseases, alcohol use, and obesity, can lead to false-positive ferritin elevations.[7]

Gene Testing and Interpretation

Biochemical screening for iron overload (TSAT or ferritin levels) is not recommended in the general population and should be performed only in patients with concern for HH. *HFE* testing is recommended in patients with biochemical manifestations of iron overload (TSAT ≥45%, increased ferritin level, or both).[1] In first-degree relatives, genotyping and measurement of TSAT and ferritin are recommended.[8] Genetic screening for HH is not recommended for the general population. The most common *HFE* variants are C282Y, H63D, and S65C. The detection of C282Y variation confirms the diagnosis of type 1 HH. Individuals with H63D and S65C variants, in the absence of C282Y, are not at risk of iron overload.[1] Testing for other non-*HFE* variants (eTable in the Supplement) in patients with iron overload in whom *HFE* variants are not identified is not recommended.[1] A proposed, but nonvalidated, diagnostic algorithm is shown in the Figure.

Patients with positive genetic testing results can be categorized into 3 disease stages, which may help clinicians monitor for disease progression[4]: stage 1, positive gene test result without iron overload; stage 2, positive gene test result with iron overload without organ damage; or stage 3, positive gene test result with iron overload and organ damage.

Role of Imaging and Liver Biopsy

Assessing hepatic iron concentration provides information regarding risk for cirrhosis.[3] Non–contrast-enhanced magnetic resonance imaging with software to estimate hepatic iron concentration can noninvasively assess iron accumulation.[5] Liver biopsy is indicated only to evaluate for alternate diagnoses, such as fatty liver disease, or to stage hepatic fibrosis if there is concern for advanced fibrosis (eg, ferritin >1000 ng/mL[1]).

No threshold level of ferritin exists for evaluating patients for cardiomyopathy. Patients with HH should be assessed for cardiac symptoms, such as chest pain, lower extremity swelling, and shortness of breath. Electrocardiogram and echocardiography may be considered to screen for subclinical arrhythmia, such as atrial fibrillation or

cardiac dysfunction, respectively. In those with positive findings, myocardial iron deposition is diagnosed with magnetic resonance imaging.[8]

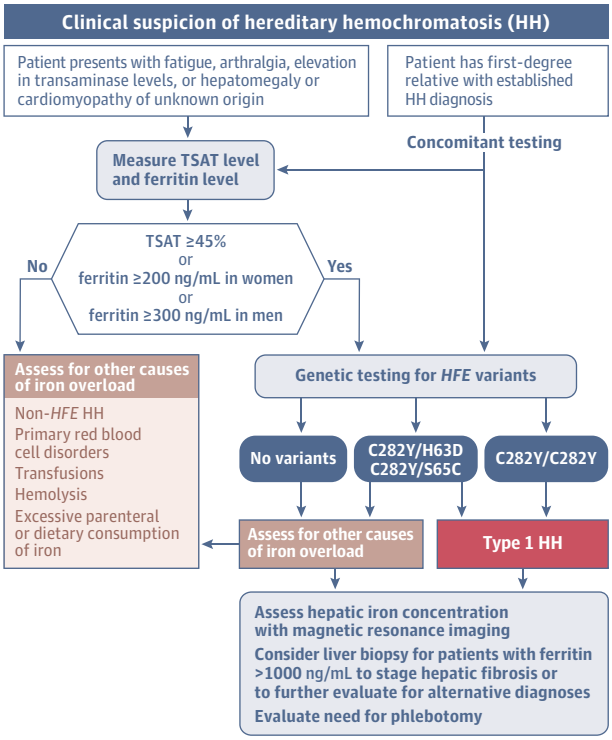
Management

Phlebotomy is first-line therapy for HH and is indicated when TSAT level is greater than 45% combined with ferritin level greater than 300 ng/mL in men or greater than 200 ng/mL in women. The benefit of phlebotomy is highest in symptomatic patients and those with ferritin level greater than 1000 ng/mL. Phlebotomy is safe, inexpensive, and generally well-tolerated, and has additional benefits because the blood removed can be used for donation.[4] As of August 1, 2022, the American Red Cross accepts blood donation from persons with HH who meet criteria for donation. Phlebotomy typically removes 500 mL of blood, which is approximately 200 to 250 mg of iron.[4] The goal of therapy is to achieve a ferritin level of 50 to 100 ng/mL without anemia, which can take several years of weekly phlebotomy. Frequency of phlebotomy can be reduced to 3 to 4 times per year once ferritin level is 50 to 100 ng/mL. In patients with stage 1 disease, yearly assessment of TSAT and ferritin levels can be performed. These patients can also be advised to regularly donate blood.[4,8]

Off-label therapy with deferasirox, an oral iron chelator approved for the treatment of secondary iron overload, may be considered in patients who are intolerant of or who do not respond to phlebotomy or when phlebotomy has potential for harm (eg, severe anemia or heart failure). However, evidence supporting efficacy of deferasirox in HH is scarce and risks and benefits must be considered. Lifestyle recommendations include maintaining a healthy body weight, avoiding iron and vitamin C supplementation, and limiting alcohol intake.[3] Alcohol may increase TSAT levels and the risk of fibrosis and HCC.[8] Patients do not need to restrict dietary iron. Proton pump inhibitors, which increase gastric pH and therefore reduce iron absorption, are supportive treatment if indicated for another condition.[8]

Phlebotomy reduces risk for cirrhosis and HCC and improves liver function, heart dysfunction, and fatigue.[9] In 106 patients with HH and advanced fibrosis treated with phlebotomy over a median of 9.5 years, 38.6% had reduction to early fibrosis.[9] HCC incidence was 2.3 per 1000 person-years vs 32.8 per 1000 person-years in those with early vs advanced fibrosis.[9] Phlebotomy does not improve diabetes, hypogonadism, or arthralgias. Patients with kidney failure or HCC should be referred for liver transplant. Liver transplant is the only curative treatment and permanently normalizes iron absorption given restoration of hepcidin levels.[1]

Figure. Proposed Diagnostic Algorithm for Assessment of Hereditary Hemochromatosis in Adults



This algorithm has not been validated for use in clinical practice. TSAT indicates transferrin saturation.

Conclusions

HH is a common and heterogeneous genetic disorder that can be diagnosed using homeostatic iron regulator gene (*HFE*) testing in patients with biochemical or clinical iron overload. Phlebotomy is first-line therapy for HH and substantially lowers risk of morbidity and mortality.

ARTICLE INFORMATION

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