



Hemochromatosis

Iron overload demands genetic testing of relatives

BY HELEN HARRISON, MSCN AND PAUL ADAMS, MD

Hereditary hemochromatosis (HH) is an autosomal recessive genetic disorder, affecting 1 in 227 people of Northern European descent. The disorder causes high iron levels and the gene responsible (HFE gene) is located on the short arm of chromosome 6, at 6p21.3. Two alleles with different point mutations account for the majority of cases, C282Y and H63D. As the condition is often silent and asymptomatic, many individuals are unaware of it and remain undiagnosed. Early treatment with therapeutic phlebotomy may prevent the development of serious life-threatening ailments, such as hepatic cirrhosis, primary liver cancer and cardiomyopathy.

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Signs and symptoms

- many remain asymptomatic
- early symptoms — fatigue and arthralgia, especially in metacarpophalangeal joints of the hand
- later complications — cirrhosis, heart failure, impotence in men, hepatocellular carcinoma
- signs
 - increased skin pigmentation, bronze or grey
 - hepatomegaly, with or without elevated liver enzymes — alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Investigations

- blood work: fasting transferrin saturation (TS) and serum ferritin (SF) levels
 - for those with a family history of HH or early symptoms
 - if SF is mildly elevated at 300-1,000 µg/L — very common; often associated with risk factors: obesity, daily alcohol consumption, inflammation and liver diseases
- genetic testing
 - if TS > 45%, and/or SF > 200 µg/L for women or 300 µg/L for men, and patient is of Northern European descent
 - to predict risk to relatives — siblings of homozygotes have a 25% chance of HH; children of C282Y/C282Y will all be carriers and have a 5% chance of having the condition themselves

Etiology

- mutated HFE protein disturbs the iron metabolism cascade and induces over-absorption
- possible pathogenesis — dysregulation of hepcidin, a liver-produced hormone controlling iron hemostasis
- most individuals with HH are homozygous C282Y/C282Y

Genetic test results

- C282Y/C282Y — C282Y homozygote — classical pattern seen in > 90% of cases; iron overload: none to massive
- C282Y/H63D — compound heterozygote — 1 copy of each mutation; most individuals have normal iron studies, a small percentage have mild-to-moderate iron overload
- H63D/H63D — H63D homozygote — 2 copies of minor mutation; iron studies: mostly normal, some with mild-to-moderate overload
- C282Y heterozygote — 1 copy of major mutation only; affects ~10% of Caucasians; iron studies usually normal, but in rare instances, can be high, in the homozygote range
- H63D heterozygote — pattern seen in ~ 20% of Caucasians; normal iron homeostasis
- no HFE mutations found
 - iron overload in patient is likely associated with mutations in other iron-related genes, e.g. transferrin receptor 2 or ferroportin
 - additional HH mutations may be discovered in the future
 - clinical history — review for other risk factors
 - liver biopsy — might determine cause of iron overload and need for treatment
 - refer to hematologist

Management

- SF > thresholds noted above — 500 mL phlebotomy done every week until SF is in low-normal range, i.e. ≤ 50 µg/L
- measure hemoglobin (Hb) level before each blood-letting — reduce frequency to once every 2 weeks if Hb < 100 g/L
- reassess SF 6 months after completing initial phlebotomies — if still rising, begin maintenance phlebotomy 3-4 times per year
- blood donation — can be done as part of maintenance phlebotomy, as long as other criteria for safe blood donation are met
- discontinue any iron-containing supplements
- limit vitamin C supplements to ≤ 500 mg per day, to prevent enhanced absorption of iron from the diet

When to refer

- Refer all the following cases to a hematologist:**
- C282Y/C282Y patients
 - risk of cirrhosis is highest with SF > 1,000 µg/L, elevated AST/ALT, and platelet count < 200 x 10⁹/L
 - regular follow-up by a liver specialist as well, if AST, ALT remain high
 - at-risk genotype and SF > 200 µg/L (women) or 300 µg/L (men) — find a centre where therapeutic phlebotomy is available, to decrease iron stores
 - also refer HH patient and family to a genetic counsellor, or at least a physician experienced with counselling people with the disorder

Phlebotomy side effects

- generally well tolerated
- possible enhanced well-being during treatment phase
- fatigue — day of phlebotomy and following day
 - encourage adequate hydration with intake of juices or sports beverages
 - tell patient to reschedule activities requiring increased exertion to non-treatment days

Population screening

- routine screening not yet suggested for North America
- the Hemochromatosis and Iron Overload Screening (HEIRS) study sampled over 100,000 participants and results are currently being evaluated

References:
Adams PC, Barton JC. Haemochromatosis. *Lancet*, 2007 (in press).
Adams PC et al. Hemochromatosis and iron-overload screening in a racially diverse population. *NEJM* 2005;352(17):1769-78.