Metal Storage Disorders
Wilson Disease and Hemochromatosis

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KEYWORDS

• Hemochromatosis • Hepcidin • Ferritin • Cirrhosis • Wilson disease • Copper

KEY POINTS

- A diagnosis of hereditary hemochromatosis (HH) usually requires an elevated serum ferritin (SF) and transferrin-iron saturation (TS) with C282Y homozygosity on *HFE* genetic testing.
- C282Y homozygous individuals with an SF level higher than 1000 μg/L have an increased risk of cirrhosis and mortality in comparison with those with an SF level lower than 1000 μg/L.
- A liver biopsy is only required in HH if SF is greater than 1000 μg/L in C282Y homozygotes or if there is suspicion of another liver disease.
- Wilson disease can present as chronic disease, acute liver failure, or acute on chronic liver disease, commonly in young individuals between 5 and 40 years of age.
- A diagnosis of Wilson disease is usually made by a combination of a low serum ceruloplasmin, increased 24-hour urine copper levels, or the presence of a Kayser-Fleischer ring on ophthalmologic slit-lamp examination.
- Liver biopsy is required in uncertain cases, although genetic testing is increasingly replacing its use as a confirmatory study, making histologic evaluation merely a staging study or a means of diagnosing concomitant liver diseases.

INTRODUCTION

Hereditary hemochromatosis (HH) and Wilson disease are metal storage disorders that result in accumulation of iron and copper, respectively, in various organs, primarily the liver. Both diseases have certain similarities such as autosomal recessive

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heritability and a variable phenotypic spectrum. A diagnosis can be made in both diseases with genetic testing. There are also significant differences between these disorders. Wilson disease has a much lower incidence, earlier age at onset and presentation, is more likely to present with symptoms, and can present with acute liver failure. By contrast, HH is a chronic disease with later age onset, lower rate of penetrance, fewer symptoms, and an expressivity that depends on multiple genetic and environmental factors. Although iron and copper cause different disorders, they can frequently affect each other's concentration in the human body. Moreover, both metals participate in redox reactions through their oxidation states (Fe^{3+}/Fe^{3+} and Cu^{2+}/Cu^{+}). Excess of these metals can lead to cell injury by oxidative stress and lipid peroxidation, which is responsible for damage to various cellular organelles such as mitochondria, lysosomes, cell membrane, and even the nuclear DNA.[1–5] These metals also work closely with each other. Ceruloplasmin, a protein that binds copper and aids in its biliary excretion, also works as ferroxidase to help utilize tissue iron. Although Wilson disease is associated with low levels of serum ceruloplasmin, a complete lack of this protein leads to an iron overload disorder called aceruloplasminemia.[6]

HEREDITARY HEMOCHROMATOSIS

HH includes a group of disorders in which the central mechanism of action involves lack of appropriate hepcidin response to body iron stores.[7] Hepcidin is a peptide hormone, encoded by a gene expressed in the liver, which controls iron absorption in the duodenum.[8] Hepcidin secretion is increased proportionately to iron absorption in duodenum, similar to the action of insulin in hyperglycemia.[9] Hepcidin prevents cellular iron export by binding to and internalizing ferroportin, which exports iron from cells.[10] The expression of hepcidin is regulated by multiple iron-sensing molecules such as BMP6 and proteins encoded by genes such as *HFE*, transferrin receptor 2 (*TFR2*), *HAMP*, and hemojuvelin (*HJV*). In HH, underlying mutations in any of these genes (or ferroportin gene) leads to a deficient hepcidin response, resulting in uncontrolled efflux of iron from enterocytes and macrophages, and iron overload in liver and other tissues.[8] It is still not clear as to how the *HFE* mutation product controls the hepcidin gene.

The most common type of HH is *HFE*-associated HH (classic or Type 1), which is responsible for most cases. The disease is autosomal recessive and involves mutations in the *HFE* gene on chromosome 6.[11] Approximately 80% to 90% of *HFE*-related HH cases are due to homozygous C282Y mutations,[8,12] whereby cysteine is replaced by tyrosine at position 282. This mutation is almost exclusively (prevalence approximately 1 in 200 to 300) seen in individuals with Northern European ancestry.[8] H63D is another *HFE* mutation associated with HH with a more global prevalence, whereby aspartic acid is substituted for histidine at position 63 of the gene.[13] However, over the last decade it has become apparent that the H63D mutation (homozygous or heterozygous) is not associated with significant iron overload.[14] Usually this is also the case among C282Y/H63D compound heterozygotes, who account for approximately 5% cases of HH and commonly develop iron overload only in the presence of another liver disease.[15,16]

Diagnosis

The diagnosis of HH is usually made by a combination of clinical features, imaging, laboratory tests, and genetic testing. The need for liver biopsy is now becoming less frequent unless a concomitant liver disease is expected or there is suspicion of cirrhosis based on other available clinical data.