

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Elevated Serum Ferritin Levels

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G&H Are there genetic or other factors that increase the susceptibility to elevated ferritin levels?

PA In a large multiethnic population, the most common causes of elevated ferritin levels are likely obesity, inflammation, and daily alcohol consumption. However, the cause of most cases of mild elevations in ferritin levels has not been clearly established, as clinicians have been reluctant to proceed to invasive testing such as liver biopsy to document iron overload.

Genetic mutations in the hemochromatosis gene (*HFE*) make up the most common genetic cause of elevated ferritin levels and are usually seen in Caucasian patients with northern European ancestors. The typical patient with hemochromatosis carries two copies of the C282Y mutation of the *HFE* gene. Mild iron overload has been demonstrated in the minority of patients with other genotypes such as H63D homozygotes or compound heterozygotes (C282Y/H63D).

G&H How are serum ferritin levels best measured?

PA Serum ferritin is a widely available enzyme-linked assay, which can be performed on a nonfasting blood sample. It is important to remember that elevated ferritin does not equal iron overload and there are many patients with elevated ferritin caused by inflammation.

G&H Can raised ferritin levels act as markers for liver disease? With which signs and symptoms are they usually associated?

PA Ferritin is stored in many types of cells, including liver cells. With liver damage from any cause, ferritin is leaked

into the blood. Therefore, serum ferritin can be an indirect measurement of liver necrosis. In the Hemochromatosis and Iron Overload Screening (HEIRS) Study, of which I am one of the principal investigators, ferritin was shown to be a surrogate marker for the presence of viral hepatitis (B and C).

It should be noted that it is not serum ferritin that leads to signs and symptoms; rather, it is the disease process that causes the ferritin elevation that may lead to signs and symptoms. It has been difficult in population screening studies to demonstrate differences in symptoms between C282Y homozygotes for *HFE* and a matched control group, demonstrating that if you set out to screen healthy people, you find healthy people.

It was estimated in a recent population study that approximately 28% of male C282Y homozygotes may have a hemochromatosis-related symptom. The most consistent abnormal finding in C282Y homozygotes is liver disease. The magnitude of the liver disease is more common in men over 50 years of age and may be accelerated if other risk factors such as alcohol, fatty liver, or viral hepatitis are also present. Nevertheless, there are some rare patients with extreme elevations of serum ferritin (>50,000 ng/mL), who are found to have histiocytosis or Still disease.

G&H At what point should patients be treated for elevated ferritin levels? What are the usual treatment options?

PA This raises an important question regarding the appropriate normal range for serum ferritin levels. Many laboratories consider serum ferritin levels greater than 200 ng/mL in women and greater than 300 ng/mL in men to be abnormal. However, a large percentage of the general population has a serum ferritin level between 200 and 1,000 ng/mL. This may be related to the epidemic of obesity and fatty liver, which may elevate ferritin levels on the basis of inflammation rather than iron overload.

If a patient is a typical C282Y homozygote for hemochromatosis, it is likely that an elevated ferritin level is related to iron overload and weekly 500 mL phlebotomy is usually recommended until the serum ferritin falls to approximately 50 ng/mL. This number was chosen because it falls within the lower spectrum of the normal

range of serum ferritin and allows for a patient who may reaccumulate iron to drift through the normal range before requiring additional phlebotomy. However, many patients, particularly women, will not show signs of iron reaccumulation, and maintenance phlebotomy may not be required for all patients. The need for maintenance can be predicted by observing the patient for 6 months after stopping phlebotomy and repeating the serum ferritin examination. In many countries, a patient at this stage can become a volunteer blood donor several times per year.

If a patient has an elevated ferritin level and is not a typical C282Y homozygote, the treatment options include observation, magnetic resonance imaging (MRI), liver biopsy, empirical phlebotomy, or voluntary blood donation. If the serum ferritin level is greater than 1,000 ng/mL, I would usually proceed directly to liver biopsy for these patients, many of whom are not found to have iron overload. MRI scanning is improving as a technique to estimate liver iron concentration, but an experienced radiologist and calibration of the scanner are required. Empirical phlebotomy can be attempted, but if the ferritin level is elevated on the basis of inflammation, the patient will likely become anemic before the ferritin level decreases. In patients with mild elevations of ferritin, observation over time may be appropriate. The measurement of transferrin saturation (TS) may also be helpful in the assessment of iron overload, although TS has wide biologic variability and a normal TS does not exclude iron overload.

G&H What has the HEIRS study revealed regarding the prevalence and characteristics of patients with elevated serum ferritin levels in the general population?

PA The HEIRS study has clearly demonstrated that there are more genes than symptoms. In typical C282Y homozygotes, approximately 20% of men and 50% of women have a normal serum ferritin level. The patients with the most iron overload in the HEIRS study were C282Y homozygous men, and non-HFE iron overload was not a common observation. HFE mutations are uncommon in non-Caucasian populations. Elevations in serum ferritin levels are commonly seen in Asians, a finding that is not likely to be related to iron overload. Genetic testing was well accepted without evidence of insurance discrimination.

G&H How prevalent has hemochromatosis been shown to be in the general population?

PA Hemochromatosis is overdiagnosed in patients who do not have the disease and underdiagnosed in those with

the disease. This is due to the common misinterpretation that an elevated serum ferritin level represents iron overload and a lack of awareness that many other types of liver disease (alcoholic liver disease, hepatitis B, hepatitis C, fatty liver) can be associated with mild-to-moderate iron overload and are commonly associated with an elevated serum ferritin level.

Many of the patients with hemochromatosis do not find their way to gastroenterology clinics because they are asymptomatic or may have fatigue and arthralgias. As with many less common diseases, the clinician must consider the possibility of the diagnosis to make the diagnosis.

G&H What do you foresee as the next steps for future research in this area?

PA In many genetic diseases, the discovery of the gene product (HFE protein) leads to the pathogenesis of the disease. This has not been the case with hemochromatosis. It appears that there is a cascade of new iron proteins such as BMP, hepcidin, hemojuvelin, and ferroportin that interact with HFE, and ongoing research may determine why some C282Y homozygotes have severe disease and others do not appear to have any abnormalities.

Suggested Reading

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