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EXPERT'S CORNER: A PERSONAL APPROACH

Iron overload

L.J. Marfil-Rivera*

Servicio de Hematología del Departamento de Medicina Interna, del Hospital Universitario ''Dr. José Eleuterio González'' UANL, Monterrey, Mexico

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The normal iron content of the body is 3–4 g. It exists in hemoglobin, in iron-containing proteins different to hemoglobin, in iron bound to transferrin in plasma, and in the form of ferritin and hemosiderin. There is approximately 1 g of storage iron, mostly in liver, spleen, and bone marrow.[1]

Iron is lost in sweat, shed skin cells, and gastrointestinal loss at a rate of approximately 1 mg/day. Menstruating women lose an additional 0.5 mg/day to 1.0 mg/day of iron.

Iron overload occurs when there is increased absorption of iron from a normal diet, or when the subject has received large doses of parenteral iron from multiple red cell transfusions or multiple infusions of intravenous iron.

Etiology

There is no mechanism for iron excretion once it has been absorbed into the body therefore iron overload is found in the following conditions.[2–4]

Increased absorption from a normal diet

Seen in the various forms of hereditary hemochromatosis, in patients with thalassemia with ineffective erythropoiesis, and in patients with congenital or acquired clonal sideroblastic anemia. In all of these conditions, there is relative or absolute deficiency of the iron-regulatory hormone hepcidin.

Hereditary hemochromatosis

In patients with homozygous hereditary hemochromatosis (HH), the absorption of iron is not regulated by serum ferritin.[5] These patients may absorb 2–4 mg of iron.[3]

Multiple infusions of iron-containing agents

Iron overload can occur secondary to multiple intravenous infusions of the following iron-containing products:

- Red cell transfusions. Each red blood cells unit contains 200 mg of elemental iron. Patients who have received more than 10 red cell transfusions are at risk of iron overload.
- Intravenous iron. Patients with renal failure and cancer patients who have been treated with multiple courses of intravenous iron in addition to erythropoiesis-stimulating agents may develop iron overload.
- Intravenous hemin/hematin. Patients with porphyria are at risk of developing iron overload because of treatment with intravenous hematin/hemin.

Liver disease

Acute and chronic liver disorders are associated with inflammation and an increase in ferritin levels, since ferritin is an acute phase reactant.

* Corresponding author at: Servicio de Hematología del Departamento de Medicina Interna, del Hospital Universitario ''Dr. José Eleuterio González'' UANL, Monterrey, NL, Mexico.
E-mail address: lmarfil@me.com

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- In alcoholic liver disease, increased levels of iron can be found, although not to the extent seen in patients with hereditary hemochromatosis.
- In patients with porphyria cutanea tarda and HCV infection, iron plays a role in the development of symptoms.
- It may not be possible distinguish some liver diseases from the liver damage seen in hereditary hemochromatosis.

Work up

Iron overload is demonstrated by serum ferritin, transferrin saturation, Magnetic Resonance Image techniques (MRI) and liver biopsy.[6] All patients suspected of having iron overload, should also be studied for HH.

Iron overload is defined by the finding of an increased transferrin saturation with an increased plasma ferritin concentration when the patient is free of inflammation. Iron overload is present when transferrin saturation exceeds 45 percent and is associated with tissue damage when it exceeds 70–75 percent.

The finding of a serum ferritin level greater than 200–300 ng/mL in men or 150–200 ng/mL in women is suggestive of iron overload. Ferritin is an acute phase reactant and serum levels may fluctuate over time, a normal level of C-reactive protein suggests that an elevated ferritin is not due to inflammation or infection. It is a poor predictor of Liver Iron Concentration (LIC) for the individual patient, and its accuracy depends on the underlying liver disease.[7–11] A high ferritin level alone is not sufficient for making the diagnosis of iron overload. It is recommended that both serum ferritin and transferrin saturation must be studied in all patients.[12]

Noninvasive imaging studies, such as CT scanning and T2 and R2 (FerriScan) measurements by MRI, have become increasingly accurate for determining hepatic and cardiac iron deposition.[6,13–22] A liver iron concentration (LIC) estimated by MRI greater than 7 mg Fe/g dry weight indicates the presence of hepatic iron overload and a cardiac T2 by MRI greater than 20 milliseconds indicates cardiac iron overload.

Parenchymal iron loading can be demonstrated semiquantitatively by Perls' Prussian blue staining of a liver biopsy specimen[23,24] and can be directly analyzed for hepatic iron content (HIC). The upper limit of normal is 1.4 mg/g to 1.8 mg/g and with any value greater than 2.0 mg/g being considered abnormal.[25,26]

When to suspect iron overload

Iron overload is suspected in relatives of individuals with hereditary hemochromatosis, in those who have received multiple red cell transfusions and those with a known disorder or clinical situation predisposing to iron overload.

Since iron overload from any cause can ultimately lead to organ failure in the heart, liver, and various endocrine organs, presence of one or more of the following signs and symptoms should also make the clinician suspect the presence of iron overload with resulting organ damage,

- Unexplained abnormalities in liver function, chronic liver disease, cirrhosis
- Cardiac enlargement with or without heart failure or conduction defects
- Diabetes mellitus
- Hypogonadism
- Skin hyperpigmentation
- Unexplained fatigue

Diagnosis

Iron overload is diagnosed by demonstrating an elevated serum/plasma ferritin along with an increased transferrin saturation on more than one occasion,

- Serum ferritin greater than 200–300 ng/mL in men or 150–200 ng/mL in women
- Transferrin saturation greater than 45 percent, and
- The following specialized tests document the presence and magnitude of iron overload
  - A liver iron concentration (LIC) estimated by MRI greater than 7 mg Fe/g dry and a cardiac T2* by MRI greater than 20 ms.
  - Levels of hepatic iron greater than 2 mg/g as obtained by liver biopsy are indicative of hepatic iron overload.[4,27]
- All patients evaluated for iron overload should have C282Y and H63D mutation analysis for diagnosing the presence (or absence) of HH.
- The finding of a C282Y/C282Y genotype confirms the diagnosis of HH.
- Heterozygote genotype (C282Y/H63D genotype) have a 60 percent of an intermediate degree of iron loading.
- Patients with a C282Y/wild type (wt) genotype are less risk of iron overload.[28]

Summary and recommendations

Iron overload is seen in a number of clinical settings; most common are multiple transfusions, liver disease, and hereditary hemochromatosis (HH).

One or more of the following signs and symptoms should make the clinician suspect the presence of organ damage secondary to iron overload

- Unexplained abnormalities in liver function, chronic liver disease or cirrhosis
- Cardiac enlargement with or without heart failure or conduction defects
- Diabetes mellitus
- Hypogonadism
- Skin hyperpigmentation
- Unexplained fatigue
- Positive family history of iron overload
- All patients suspected of having iron overload should have iron studies as well as genetic testing.
- Serum ferritin greater than 200–300 ng/mL in men or 150–200 ng/mL in women and/or a transferrin saturation greater than 45 percent indicates iron overload.
- A choice among these options:
  - A liver iron concentration estimated by MRI greater than 7 mg Fe/g dry weight indicates the presence of

hepatic iron overload and a cardiac T2* over 20 milliseconds indicates the presence of cardiac iron overload
  - A liver biopsy performed specifically for the determination of iron overload is rarely needed.
- All patients being evaluated for iron overload should have C282Y and H63D mutation analysis.

Conflict of interest

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