Ferritin

Marilyn Zeman
November 2013
GI for GPs

Objectives

- Outline the causes and complications of hyperferritinemia and iron overload syndromes.
- Identify when an elevated ferritin suggests hereditary hemochromatosis and when treatment is required.

Faculty Disclosure

- Faculty: Marilyn Zeman
- Relationships with commercial interests:
  - Grants/Research Support: none
  - Speakers Bureau/Honoraria: none
  - Consulting Fees: none
  - Other: none
Iron absorption and distribution

**Step 1.** Iron is converted to Fe^2+ in the stomach and binds to gastroferritin.

**Step 2.** In duodenum, Fe^2+ is released from gastroferritin, is absorbed and binds to transferrin.

**Step 3.** In liver, some Fe^2+ is released and binds to apoferritin to be stored as ferritin.

- **TIBC (total iron binding capacity):** an indirect measure of transferrin in serum.
- **Tsat= serum Fe/TIBC x 100:** Transferrin iron saturation index (Tsat); the amount of iron bound to transferrin.
- **Ferritin:** an indirect measure of iron stores.

With Hereditary Hemochromatosis can absorb up to ~4 mg/day

↑ Absorption of iron → ↑ tsat → ↑ iron deposition in organs → ↑ ferritin

no physiologic pathway for excretion of iron
It is estimated that ~90% of patients with hyperferritinemia seen in routine medical practice do not have iron overload.

Adams & Barton, 2011
Hyperferritinemia with iron overload

Iron indices in iron overload*

<table>
<thead>
<tr>
<th>Transferrin saturation</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 45%</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ferritin</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 300 μg/L</td>
<td>50</td>
<td>88</td>
</tr>
</tbody>
</table>

*In C282Y/C282Y

Must consider:
1. Ferritin is an acute phase reactant. In iron overload becomes abnormal only when loading has advanced to liver involvement.
2. Transferrin saturation is the ratio of serum Fe and transferrin, and therefore is impacted by situations which effect these variables, ex. alcohol → ↑Fe absorption → ↑Tsat. Chronic liver disease ↓ transferrin synthesis → ↓transferrin (ie. TIBC) → ↑Tsat.

↑Ferritin

Non-Iron overload

Ex. Acute and chronic inflammation

Primary or idiopathic

Ex. Hereditary hemochromatosis (HH)

Iron overload

secondary

Ex. Transfusions, non HH liver diseases, etc

miscellaneous

Ex. African iron overload

Non-Iron overload

Ex. Neonatal iron overload

Aceruloplasminemia

Congenital transferrinemia

Tavill et al. AASLD 2001
Secondary Causes of Iron Overload

- Iron is deposited in Kupffer cells (macrophages of liver) and is mild.
- Kupffer cell iron loading is relatively innocuous (called hemosiderosis).
- When iron burden overwhelms ability of Kupffer cells to sequester iron, hepatocyte iron overload develops.
- Then, secondary iron overload can lead to liver disease, similar to that seen in primary iron overload.

Therefore can have iron overload without hepatic damage.

Secondary causes of iron overload

- Examples:
  - Iron loading anemias and transfusion:
    - thalassemia major
    - sideroblastic anemia
    - chronic hemolytic anemia
  - Dietary and transfusional iron overload
  - Chronic liver disease (alcohol, NASH, HCV, HBV)
  - Insulin resistance
  - Porphyria cutanea tarda

Treatment of hemosiderosis and secondary iron overload: treat condition. If not enough, remove iron with phlebotomy and/or iron chelation drugs depending on anemia and tolerability.

Primary/Idiopathic Causes of Iron Overload

- Hereditary hemochromatosis
  - HFE related
    - C282Y/C282Y
    - C282Y/H63D
    - Other HFE mutation
  - Non-HFE related
    - Hemochromatosis (HJV)
    - Transthyretin (TTR)
    - Ferritin (SCL40A1)
    - Hepcidin (HAMP)
    - African iron overload

*account for <5% of cases encountered.
HFE- Hereditary Hemochromatosis

- Autosomal Recessive trait.
- HFE prevalence 1/150-1/200 of Northern European descent.\(^1\)
- Effect is unregulated increased Fe absorption from duodenum.
- Ferritin >1000 predicts presence of cirrhosis.\(^2\)
- Individuals with asymptomatic HH and ferritin <1000 at low risk for developing signs and symptoms in the future.\(^3\)

\(^1\) Bacon. 2001; \(^2\) Beaton et al. 2002; \(^3\) Beutler et al. 2002

Phenotypic expression of HFE-HH

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y/C282Y</td>
<td>50% of women and 20% of men have normal ferritin and never require therapy. Disease rarely presents in people younger than 40 yr old. 50% penetrance.</td>
</tr>
<tr>
<td>C282Y/H63D</td>
<td>Most have normal iron levels. Moderate iron overload can develop if other risk. (^4) (&lt;1% penetrance.</td>
</tr>
<tr>
<td>C282Y/normal</td>
<td>10% of Caucasians. Most have normal iron levels. Rarely develop iron overload without other risks. (^5)</td>
</tr>
<tr>
<td>H63D/H63D</td>
<td>Most have normal iron but mutation may be associated with increased I f levels. Iron overload depends on other risks. (^6)</td>
</tr>
<tr>
<td>H63D/normal</td>
<td>20% of Caucasians. Iron overload unlikely. If overload seen consider other causes.</td>
</tr>
</tbody>
</table>

\(^4\) Gochee et al. 2002

C282Y/C282Y in absence of elevated iron is not diagnostic for HH. It represents a genetic susceptibility to develop it in future.
Diagnosis of iron overload and determination of cause

- History and blood work
- Genetics
- Liver biopsy
  - Iron in hepatocytes vs macrophages
  - Grade fibrosis
  - Determine Hepatic Iron Index (HII) (need to specify on path req.)
- MRI (FerriScan®)
- Quantitative phlebotomy
Quantitative phlebotomy

- 500 ml phlebotomy removes 200-250 g of mobilizable body iron and decreases serum ferritin ~25 ng/mL.
- therefore if ferritin 1000, need 40 phlebotomies.
- Patient without significant iron overload cannot tolerate weekly phlebotomies
  - become deficient in 4-5 phlebotomies over 4-8 weeks.

Munoz et al. 2011

Summary- Common clinical scenario #1 (my approach)

- 40 yr old obese man with DM, dyslipidemia, ALT 90, AST 80, ferritin 300. No previous blood work.
- Is this elevated ferritin from HH or metabolic syndrome?

Approach:

- Check tsat
  - ↑ tsat more consistent with HH but normal in metabolic syndrome.
  - Some would also suggest check ESR and CRP.
  - These could be up in inflammation but correlation with ferritin inconsistent.
- Send genetic testing
  - Even if tsat normal, AASLD guidelines suggest testing. But even if HH genotype found, may not have phenotype.
- Follow blood work with weight loss as first step.
  - Ferritin and liver tests do not vary with HH and would not improve with weight loss if due to HH.

Summary- common clinical scenario #2 (my approach)

- 40 yr old C282Y/H63D alcoholic with ALT 130, AST 100, ferritin 1000, tsat 60%
- Is this elevated ferritin from HH or alcoholism?

Approach:

- Follow blood work with alcohol abstinence.
  - If it because of alcohol use expect blood work to improve
- Quantification of liver iron with biopsy, or alternatively with MRI or quantitative phlebotomy.
  - Liver biopsy could tell you if iron is in macrophages, hepatocytes or both. Only if iron is in hepatocytes would phlebotomy be needed. Biopsy can also tell you if evidence of fibrosis/cirrhosis, and can give quantification of iron.
  - MRI can also quantify iron load.
  - Quantitative phlebotomy (if unable to have biopsy or MRI), if patient becomes anemia within a few phlebotomies then not iron overload.
Complications of HFE-HH

Secondary hyperparathyroidism: presents as fatigue, impotence, osteoporosis - fatigue improves with therapy, impotence rarely improve with therapy.

Skin pigmentation: rarely seen - generally improves with therapy.

Liver cirrhosis and HCC: presents as fatigue, impotence, amenorrhea, osteoporosis - fatigue improves with therapy, impotence rarely improves with therapy.

Arthropathy: pseudogout, chondrocalcinosis, chronic arthropathy - usually 2nd and 3rd MCP and ICP - may be better, worse or same with therapy.

Diabetes Mellitus: some improvement in blood glucose levels and decreased insulin requirements with therapy.

Secondary hypogonadism: presents as fatigue, impotence, amenorrhea, osteoporosis - fatigue improves with therapy, impotence rarely improves with therapy.

Primary hypothyroidism: may or may not improve with therapy.

Skin pigmentation: rarely seen - generally improves with therapy.

Liver fibrosis in 5-20%¹

Cirrhosis in 2-6%¹

>60 g/d alcohol increases risk of cancer by 9 fold²

Hepatocellular cancer in 30-50% cirrhotics

Death from cirrhosis complications 20%³

- Risk factors for HCC include cirrhosis, severity, advanced age, alcoholism, smoking, HBV/HCV infection.
- Partial evacuation can reverse fibrosis but does not reverse cirrhosis and does not decrease risk of cancer.

¹: Powell et al. 2006
²: Fletcher et al. 2002
³: Harrison & Bacon, 2005
⁴: Adams, 1997
Genetic Hemochromatosis

<table>
<thead>
<tr>
<th>HI type</th>
<th>HFE</th>
<th>HFE</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IA</th>
<th>Type IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>HFE</td>
<td>HFE</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td>Frequency</td>
<td>Frequent</td>
<td>Limited cases</td>
<td>Limited families</td>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic background</td>
<td>Northern European</td>
<td>Southern European</td>
<td>Japanese</td>
<td>Southern European</td>
<td>Northern European</td>
<td>Southern European</td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Ubiquitous</td>
<td>Ubiquitous</td>
<td>Heart failure, hypogonadism</td>
<td>Ubiquitous</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Anguilar-Martinez et al. 2005

Other Causes of Hereditary Hyperferritinemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial dysproteinemia</td>
<td>AD</td>
<td>Anemia, malabsorption, liver disease</td>
</tr>
<tr>
<td>Hereditary Hyperferritinemia</td>
<td>AD</td>
<td>Early bilateral osteoarthritis, iron overload</td>
</tr>
<tr>
<td>Hereditary Hyperferritinemia-</td>
<td>AR</td>
<td>Severe anemia, iron overload</td>
</tr>
<tr>
<td>Disease</td>
<td>AR</td>
<td>Anemia, neurological symptoms, iron overload</td>
</tr>
<tr>
<td>Aceroelastinemia</td>
<td>AR</td>
<td>Anemia, neurological symptoms, iron overload</td>
</tr>
<tr>
<td>DMT1 disease</td>
<td>AR</td>
<td>Anemia, neurological symptoms, iron overload</td>
</tr>
<tr>
<td>Mitochondrial iron overload</td>
<td>?</td>
<td>Iron overload</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>?</td>
<td>Liver failure, iron overload</td>
</tr>
</tbody>
</table>

American Association for the Study of Liver Disease (AASLD) screening guidelines for Hereditary Hemochromatosis

No evidence for universal screening

AASLD. Hepatology 54(1), 2011
Treatment of iron overload

- Iron depletion improves quantity and quality of life
  - Phlebotomy
    - Tsat usually remains elevated until iron stores are depleted.
    - Ferritin may fluctuate and eventually falls.
    - In HH, some, especially women, may never reaccumulate iron after phlebotomy to depletion.

  Crosby et al. 1986

<table>
<thead>
<tr>
<th>Hematocrit/hemoglobin</th>
<th>Use phlebotomy (removal of 500 ml, blood) weekly or biweekly</th>
<th>( \text{Hemoglobin} \times 100 )</th>
<th>( \text{Hematocrit} \times 100 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check hematocrit/hemoglobin prior to each phlebotomy.</td>
<td>Allow hematocrit/hemoglobin to fall by no more than 3% of prior level.</td>
<td>Check serum ferritin level every 10-12 phlebotomies.</td>
<td>Stop frequent phlebotomy when serum ferritin reaches 50-100 ( \mu )g/L.</td>
</tr>
<tr>
<td>Continue phlebotomy at intervals to keep serum ferritin between 50 and 100 ( \mu )g/L.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

  AASLD. Hepatology 54(1), 2011

- Iron chelating drugs (2nd line if phlebotomy not an option)
  - Deferoxamine: poor compliance in HH
  - Deferasirox, deferiprone: need more studies in HH

- Dietary management
  - No need to avoid meat
  - Limit intake of supplement of vitamin C to 500 mg/d
  - Avoid iron supplementation
  - Avoid alcohol
  - Avoid shellfish (vibrio vulnificus, Yersinia enterocolitica, listeria infections have been documented, as they are "iron-loving" organisms)

  Adams & Barton, 2010

Summary

- Ferritin is a maker of iron stores, but may be falsely elevated in infection/inflammation.
  - Especially if acute, fluctuating, <1000 ng/mL.

- Transferrin saturation more specific marker of iron overload.

- Genetic iron overload seen with C282Y/C282Y and possibly C282Y/H63D
  - Penetrance is low and having genetic susceptibility does not mean somebody will develop disease.
  - Consider other risk factors for iron overload in other genotypes and try to eliminate these risk factors.
Summary

- In HH iron overload, symptoms and abnormal liver tests develop over decades.
- Iron overload diagnosed by liver biopsy, MRI, quantitative phlebotomy.
- Phlebotomy treatment only indicated in those with diagnosed hepatic iron overload.
- If phlebotomy not an option or not tolerated, iron chelation drugs are an option.