Blood Day for Primary Care

What should I do to investigate a high ferritin?

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Disclosures

No relevant disclosures
Objectives

1. Develop working knowledge of iron homeostasis and storage as it relates to ferritin

2. Develop a broad differential diagnosis for an elevated ferritin in an adult patient

3. Clarify utility of HFE gene testing in selected individuals

4. Clarify the role of phlebotomy in patients with iron overload
Interactive question

1. Which of the following is the most common cause of an elevated ferritin in a patient presenting to your practice?
   
a) Hepcidin mutation
   
b) HFE C282Y/C282Y mutation
   
c) Inflammation
   
d) Transfusion support
Dear Dr.,

Thank you for seeing [redacted], a 42 year old male patient. He has been having markedly increased ferritin levels with his last level being 1013. His Iron was 35 and TIBC was 52. He also had a CXR and CT abdomen done that was normal. The patient denies any joint pains and his physical examination was essentially normal. He is also awaiting and allergist review for large unexplained hives/urticaria that he gets all over his body at times. I will attach copies of his results. Your review of this patient and advise on management is appreciated.

Active Medications: EXPIRED LOSEC 20 MG DELAYED RELEASE CAPSULE EXPIRED 1 CAP QD 1 MO30
DICLOFENAC 4% GEL AND LIDOCAINE 2% GEL 1 APPLN BID PRN 1 MO30 As directed
elbow brace - narrow see instructions for tennis elbow right arm
Physiotherapy see instructions For right tennis elbow
EXPIRED BETADERM VALERATE 0.1% TOPICAL CREAM EXPIRED 1 APPLN BID PRN 30 Day
EXPIRED NIX CREAM RINSE TOPICAL SOLUTION EXPIRED 1 APPLN QD 1 Day Aply from head to toe and leave on for 8 hours

Allergies: No Allergies recorded
Medical History: mildly elevated lipids

Family History:

Sincerely,
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALKALINE PHOSPHATASE</td>
<td>63</td>
<td>30 - 135</td>
<td>u/L</td>
</tr>
<tr>
<td>GGT</td>
<td>80</td>
<td>0 - 50</td>
<td>u/L</td>
</tr>
<tr>
<td>AST</td>
<td>49</td>
<td>0 - 35</td>
<td>u/L</td>
</tr>
<tr>
<td>ALT</td>
<td>75</td>
<td>10 - 40</td>
<td>u/L</td>
</tr>
<tr>
<td>IRON</td>
<td>35</td>
<td>5 - 30</td>
<td>u/L</td>
</tr>
<tr>
<td>TIBC</td>
<td>52</td>
<td>50 - 150</td>
<td>umol/L</td>
</tr>
<tr>
<td>FERRITIN</td>
<td>1013</td>
<td>22 - 430</td>
<td>ng/mL</td>
</tr>
<tr>
<td>B12</td>
<td>974</td>
<td>123 - 830</td>
<td>pmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>1.2</td>
<td>0.4 - 4.2</td>
<td>mIU/mL</td>
</tr>
<tr>
<td>FREE T4</td>
<td>13.7</td>
<td>7.7 - 9.7</td>
<td>pmol/L</td>
</tr>
<tr>
<td>FREE T3</td>
<td>6.0</td>
<td>3.7 - 6.2</td>
<td>pmol/L</td>
</tr>
</tbody>
</table>
REQUEST FOR CONSULTATION

To: St. Boniface Hospital

Hematology

Fax Number: 786-0621

CONSULTATION DATE:

DATE: ____________

TIME: ____________

NO SHOW FEE: _____

(lives in a group home)

Family history:

Hematological:

Other:

Lived in a group home

Please review and advise

Thank you
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>18</td>
<td>9 - 30 umol/L</td>
</tr>
<tr>
<td>Iron Binding (TIBC)</td>
<td>29</td>
<td>45 - 81 umol/L</td>
</tr>
<tr>
<td>Ferritin</td>
<td>1041</td>
<td>&lt; 12.0 ug/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.0 - 30.0 ug/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31.0 - 79.0 ug/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80.0 - 300.0 ug/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 300.0 ug/L</td>
</tr>
</tbody>
</table>

Iron deficient                  Depleted iron store                Reduced iron stores                Normal iron stores                Likely iron overload
Work-Up of HIGH FERRITIN

Elevated Ferritin

Is there a concurrent inflammatory illness?

YES

Clinical assessment & repeat ferritin when illness resolves

NO

Transferrin Sat > 45%

YES

Caucasian?

NO

Clinical Suspicion of liver disease and/or abnormal LEs / LFTs?

NO

PO / IV / IM iron?

YES

Appropriate clinical / laboratory / imaging evaluation. Consider referral to Specialist for additional work-up

NO

Discontinue iron supplementation if indicated and retest ferritin

NO

Anemia and/or Transfusion dependence

YES

Referral to CCMB Hematology for:
- Anemia work-up
- Iron chelation

NO

Referral to CCMB Hematology for:
- Trial of Phlebotomy

NO

No Further work-up

NO

C282Y or C282Y1 / H63D

YES

Referral to CCMB Hematology for:
- Trial of Phlebotomy

NO

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
Reason for ordering test?
Testing clinically indicated for IDA, screening family members and as diagnostic criteria in specific inflammatory disorders.
Work-Up of HIGH FERRITIN

Elevated Ferritin

- Is there a concurrent inflammatory illness?
  - YES
    - Clinical assessment & repeat ferritin when illness resolves
      - Is ferritin still elevated?
        - NO
          - No Further work-up
        - YES
          - Referral to CCMB Hematology for: Trial of Phlebotomy
  - NO
    - Transferrin Sat > 45%
      - YES
        - Appropriate clinical laboratory imaging evaluation. Consider referral to Specialist for additional work-up
      - NO
        - Clinical Suspicion of iron overload
          - YES
            - Discontinue iron supplementation if indicated and retest ferritin
          - NO
            - Referral to CCMB Hematology for:
              - Anemia work-up
              - Iron chelation

- Caucasian?
  - YES
    - C282Y or C282Y/H63D
      - YES
        - Referral to CCMB Hematology for: Trial of Phlebotomy
      - NO
        - Anemia and/or Transfusion dependence
          - YES
            - Referral to CCMB Hematology for:
              - Anemia work-up
              - Iron chelation
          - NO
            - Referral to Specialist for:
              - MRI liver
              - Liver biopsy
              - Phlebotomy
              - Iron chelation

Ferritin = stored iron
Measured ferritin = serum ferritin
Serum ferritin approximates tissue ferritin under stable conditions
Tissue ferritin = tissue iron
Increased tissue iron = organ damage
Gold standard vs. surrogate markers of tissue iron
Serum iron + TIBC = iron in transit
Transferrin sat = Serum iron/TIBC
Only 1 in 10 patients with elevated ferritin have true tissue iron overload.

**Work-Up of HIGH FERRITIN**

1. Elevated Ferritin
   - Is there a concurrent inflammatory illness?
     - **YES**: Clinical assessment & repeat ferritin when illness resolves
     - **NO**: Transferrin Sat > 45%
       - **YES**: Caucasian?
         - **YES**: C282Y or C282Y/H63D
           - **YES**: Appropriate clinical laboratory / imaging evaluation. Consider referral to Specialist for additional work-up
           - **NO**: Discontinue iron supplementation if indicated and retest ferritin
         - **NO**: Clinical Suspicion of liver disease and/or abnormal LEs / LFTs?
           - **YES**: PO / IV / IM iron?
             - **YES**: Referral to CCMB Hematology for:
               - Anemia work-up
               - Iron chelation
             - **NO**: Referral to CCMB Hematology for:
               - Anemia work-up
               - Iron chelation
           - **NO**: Referral to Specialist for:
             - MRI liver
             - Liver biopsy
             - Phlebotomy
             - Iron chelation
       - **NO**: Is ferritin still elevated?
         - **YES**: No Further work-up
         - **NO**: No Further work-up
**Work-Up of HIGH FERRITIN**

- Elevated Ferritin
  - Is there a concurrent inflammatory illness?
    - YES
    - Sensitivity 0.70
    - Specificity 0.89
    - Only for C282Y
    - Transferrin Sat > 45%
    - White 2.4%
    - Hispanic 1.3%
    - Asian 0%
    - Black 0.27%
    - Weekly phlebotomy 500ml = 250mg iron
    - Keep Hgb > 120 pre Target ferritin 50-100
    - Chelation in select Organ damage?
    - Family counseling
  - NO
    - C282Y or C282Y/H63D
    - Clinical Suspicion of liver disease and/or abnormal LEs / LFTs?
      - YES
      - Appropriate clinical laboratory / imaging evaluation. Consider referral to Specialist for additional work-up
      - Discontinue iron supplementation if indicated and retest ferritin
      - Anemia and/or Transfusion dependence
        - Referral to CCMB Hematology for:
          - Anemia work-up
          - Iron chelation
        - Referral to Specialist for:
          - MRI liver
          - Liver biopsy
          - Phlebotomy
          - Iron chelation
    - NO
    - Referral to CCMB Hematology for: Trial of Phlebotomy
      - NO
      - No Further work-up

February 5, 2013: Hematology, USG/TINAL (Ponnampalam)
Work-Up of HIGH FERRITIN

- Elevated Ferritin
  - Is there a concurrent inflammatory illness?
    - YES
    - Transferrin Sat > 45%
      - YES
      - Clinical Suspicion of liver disease and/or abnormal LEs / LFTs?
        - YES
        - PO / IV / IM iron?
          - YES
          - Anemia and/or Transfusion dependence
            - YES
            - Referral to Specialist for:
              - MRI liver
              - Liver biopsy
              - Phlebotomy
              - Iron chelation
            - NO
            - Referral to CCMB Hematology for:
              - Anemia work-up
              - Iron chelation
          - NO
          - Discontinue iron supplementation if indicated and retest ferritin
            - YES
            - Referral to CCMB Hematology for:
              - Anemia work-up
              - Iron chelation
            - NO
            - Fatty liver
              - Alcohol
              - Viral
              - Auto-immune
              - Etc...
      - NO
      - Caucasian?
        - YES
        - C282Y or C282Y/H63D
          - YES
          - Appropriate clinical / laboratory / imaging evaluation. Consider referral to Specialist for additional work-up
            - NO
            - No Further work-up
        - NO
        - Is ferritin still elevated?
          - YES
          - No Further work-up
          - NO
          - Clinical assessment & repeat ferritin when illness resolves

- Ferritin > 1000 increases risk for fibrosis / cirrhosis
Work-Up of HIGH FERRITIN

Elevated Ferritin

Is there a concurrent inflammatory illness?

YES

Clinical assessment & repeat ferritin when illness resolves

Is ferritin still elevated?

YES

Referral to CCMB Hematology for:
  • Trial of Phlebotomy

NO

NO

No Further work-up

Caucasian?

YES

C282Y² or C282Y¹ H63D

NO

Clinical Suspicion of liver disease and/or abnormal LEs / LFTs?

YES

Appropriate clinical / laboratory / imaging evaluation. Consider referral to Specialist for additional work-up

NO

PO / IV / IM iron?

YES

Discontinue iron supplementation if indicated and retest ferritin

NO

Anemia and/or Transfusion dependence

YES

Referral to CCMB Hematology for:
  • Anemia work-up
  • Iron chelation

NO

Referral to Specialist for:
  • MRI liver
  • Liver biopsy
  • Phlebotomy
  • Iron chelation

Optimal timing of serum iron tests?
Work-Up of HIGH FERRITIN

Elevated Ferritin

Is there a concurrent inflammatory illness?

YES

Clinical assessment & repeat ferritin when illness resolves

NO

Is ferritin still elevated?

YES

 NO

Caucasian?

YES

Clinical suspicion of liver disease and/or abnormal LEs / LFTs / imaging

NO

C282Y or C282Y/H63D

YES

NO

Appropriate clinical laboratory / imaging evaluation. Consider referral to Specialist for additional work-up

Referral to CCMB Hematology for:
- Trial of Phlebotomy

NO

Transferrin Sat > 45%

YES

NO

1 RBC unit = 250mg iron

Iron loading” Anemia

PO / IV / IM iron?

YES

NO

Discontinue iron supplementation if indicated and retest ferritin

Anemia and/or Transfusion dependence

Referral to CCMB Hematology for:
- Anemia work-up
- Iron chelation

Referral to Specialist for:
- MRI liver
- Liver biopsy
- Phlebotomy
- Iron chelation

NO

No Further work-up
Work-Up of HIGH FERRITIN

Elevated Ferritin

Is there a concurrent inflammatory illness?

YES
Clinical assessment & repeat ferritin when illness resolves

NO

Transferrin Sat > 45%

Caucasian?

YES

C282Y² or C282Y1/H63D

NO

Clinical Suspicion of liver disease and/or abnormal LEs / LFTs?

NO

PO / IV / IM iron?

YES

Discontinue iron supplementation if indicated and retest ferritin

NO

Anemia and/or Transfusion dependence

YES

Referral to CCMB Hematology for:
- Anemia work-up
- Iron chelation

NO

Referral to Specialist for:
- MRI liver
- Liver biopsy
- Phlebotomy
- Iron chelation

NO

Is ferritin still elevated?

NO

No Further work-up

YES

Referral to CCMB Hematology for:
- Trial of Phlebotomy

February 3, 2015: Hematology DSG FINAL (Ponnampalam)
Take Home Messages

• 1 in 10 patients with elevated ferritin have tissue iron overload

• Common causes of elevated ferritin are inflammatory disorders and liver diseases

• Phlebotomy is the mainstay of treatment for patients with tissue iron overload
Questions?

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