Approach to a high ferritin level: the hepatologist’s perspective

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Hepatology day, LSGE

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FERRITIN

- Major storage protein for iron
- Present in large amounts in macrophages and hepatocytes (storage)
- In erythroblasts (for metabolic purposes)
- Small concentrations in plasma (not transport protein like transferrin) → reflects total iron body stores
- Most widely used surrogate for iron overload (highly sensitive in Hemochromatosis), low specificity.
HYPERFERRITINEMIA: etiology

• Increased ferritin synthesis
  Acquired or genetic conditions, with or without iron overload

• Increased ferritin release
  From damaged cells: steatosis, steatohepatitis, chronic viral hepatitis, liver necrosis, acute hepatitis, acute MI, splenic infarct

• Clue: clinical setting
HYPERFERRITINEMIA: etiology

Iron overload

- Primary:
  - Hereditary hemochromatosis
  - Hereditary aceruloplasminemia
- Secondary:
  - Transfusion overload
  - Excess dietary iron
  - Porphyria cutanea tarda
    - Cutaneous photosensitivity
    - Hepatic iron overload
    - Urinary and fecal porphyrin excretion
  - Ineffective erythropoiesis (sideroblastic anemia)

Liver diseases / Acute inflammation

- NASH / NAFLD
- Viral hepatitis
- Familial hyperferritinemia-Cataract syndrome

Alcohol excess

- Regular consumption: disruption of normal iron metabolism
- Excess deposition of iron in liver in 1/3 of alcoholic patients

Adams PC, J Hepatol, Feb. 2011
HYPERFERRITINEMIA

• > 90% of outpatients:
  – Chronic alcohol intake
  – Inflammation (CRP)
  – Cell necrosis (TA-CK)
  – Malignancy (ESR, imaging)
  – NAFLD and/or
  – Metabolic syndrome (HTN, BMI, Chol, TGL, Glucose)

• Often measured if:
  – Persistent elevation despite treatment
  – Investigate fatigue, possible liver disease, anemia or neoplasia.
Reference concentration of ferritin

• Variable (lab, personal)
• Large multi-ethnic multi-racial screening study of iron overload north americans patients:
  > 300 µg/L in males
  > 200 µg/L in females
• Mean SF - % of patients with high SF
  – Higher in blacks, asians, pacific islanders vs. whites
• Transferrin saturation:
  – TS > 50 % in males, > 45 % in females
  – TS higher in asians, lower in african americans
⇒ Elevated SF and TS are not always indicators of disease


Never test Ferritin/TS in acutely ill patients:
- Ferritin misleadingly high
- TS conversely low, may mask iron overload
Use of Transferrin saturation to interpret serum ferritin

• Clinicians rely on TS to interpret elevated ferritin levels:
  – Iron overload
  – Iron deficiency
  – Subnormal iron mobilization for erythropoiesis
• Reliability not 100% accurate
• Large population screening cohort ➔ significant biological variability in serum TS
Use of Transferrin saturation to interpret serum ferritin

- 64230 patients
  - Non-fasting TS >45 % (males) and >50% (females)
    - **Se 75% Sp 95%** in detection of C282Y homozygotes
      (fasting failed to increase sensitivity)
- ↓ reliability and specificity of TS in clarifying significance of high ferritin levels
- Acute infection / Menses / recent blood donation may decrease TS temporarily in patients with hepatic iron overload.

Relationship between TS and liver iron concentrations

- TS predicts hepatic iron overload better in C282Y homozygotes.

- Some patients with normal TS and high ferritin may have hepatic iron overload (proven by histology)

High Ferritin

High TS

MRI: assess liver concentration, Fe distribution (spleen, pancreas)

Liver biopsy: steatosis, steatohepatitis, fibrosis

Normal TS

Iron Overload

No Iron overload

Question?
High ferritin, normal TS

Useful to measure

- AST, ALT → hepatocyte necrosis, iron overload
- U/S liver → fatty liver, steatohepatitis
- Alcohol consumption → history, GGT
- HBsAg, HCV Ab → ↑ ferritin without Fe overload
Common causes

- Normal TS, no iron overload
- Liver diseases
  - NASH
  - Viral hepatitis
- Chronic inflammatory conditions
  - Rheumatoid arthritis
  - IBD
  - Bacterial infections
- Malignancies (esp. hematologic)
- Thyrotoxicosis
- Excessive Alcohol intake
Normal TS, no iron overload

**HEREDITARY HYPERFERRITINEMIA-CATARACT SYNDROME**

- Up-regulation of L-Ferritin
- Constantly elevated ferritin levels
- No iron overload
- L-ferritin deposition in ocular lens causing bilateral cataract at early age


**DYSMETABOLIC SYNDROME**

- Metabolic syndrome:
  - Obesity, Dyslipidemia
  - Diabetes, Hypertension
- Liver biopsy: Iron deposition in Kupfer cells (peri-portal-hepatocytic in HFE-HC) / steatosis
- No iron overload
ACERULOPLASMINEMIA
- Rare genetic syndrome
- Mutation in gene that encodes for ceruloplasmin
- Retinal abnormalities
- Neurologic manifestations (dementia, cerebellar ataxia)
- Vs. Wilson’s:
  - Absence of ceruloplasmin in serum
  - Absence of excess copper storage in liver
  - Absence of excess Urubber

FERROPORTIN DISEASE
- Mutation of SLC40A1 encoding for ferroportin
- Rare, autosomal dominant
- Significant liver iron deposition
Liver biopsy

- Well established tool for evaluation of iron overload + concomittant liver diseases
- In normal TS patients, indication to biopsy:
  - High SF and presence of confounding factors
  - Exclude iron overload
  - Stage, diagnose liver disease
- Not routinely recommended to assess Fe overload if SF < 1000 µg/L
Liver biopsy in confirmed hepatic overload

- Limited indication
- With availability of HFE-genotyping:
  - Homozygous C282Y + high iron body stores enough for diagnosis of HFE-HC
  - Histology only to grade degree of fibrosis
- In C282Y homozygous patients, if:
  - Normal liver/Ferritin < 1000 µg/L/normal AST
    $\Rightarrow$ NPV $\sim$ 95% for significant liver fibrosis
- If 1, 2 or all criteria not met $\Rightarrow$ High risk of fibrosis

Fibrosis regression: role for liver biopsy

- 36 C282Y homozygous patients
- Severe fibrosis: bridging fibrosis to cirrhosis
- Regression noted in 69% of F3 vs. 35% of F4
  
  Falize J, Hepatology 2006;44:472-477

- Improvement / resolution of esophageal varices reported with phlebotomy
  
Fig. 3. Proposed algorithm for the diagnosis of genetic causes of hyperferritinemria.
Iron overload disorders
High ferritin, high TS
Iron metabolism

- Fe reutilized in closed circuit
- Central role of liver through hepcidin production
- Hepcidin: major regulator of intestinal iron and iron delivery to plasma
- Hepcidin controls iron transport into duodenum and iron export in macrophages
- Hepcidin degrades ferroportin (transport) → blocks Fe release from cells to plasma
Pathophysiology of iron overload disorders

- Hepcidin deficiency: central pathogenic factor in HC
- Unrestricted flow of iron into the plasma iron pool
- Some taken up by bone marrow, some stored in hepatocytes as ferritin
# Genetic Iron overload disorders

<table>
<thead>
<tr>
<th>HEMOCHROMATOTIC</th>
<th>NON-HEMOCHROMATOTIC</th>
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<tbody>
<tr>
<td>• Normal erythropoeisis</td>
<td>• Type A ferroportin disease</td>
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<tr>
<td>• Parenchymal Fe distribution related to hepcidin dysfunction</td>
<td>• Hereditary aceruloplasminemia</td>
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<td>HFE-HC (type 1)</td>
<td>• Hereditary atransferrinemia</td>
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<td>JUVENILE HC (type 2)</td>
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<td>Transferrin Rec 2 TFR2 (type 3)</td>
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<tr>
<td>Type B ferroportin disease</td>
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Acquired iron overload disorders

- Chronic excessive iron supply
- Hematologic disorders
  - Thalassemia
  - Myelodysplastic syndrome
  - Sickle cell anemia
- Chronic liver diseases
  - Destruction of hepatocytes
  - Decreased hepcidin
Unexplained symptoms, signs, or diseases suggestive of hemochromatosis in adults

Check TS and SF

TS high, SF high
- Caucasians
  - HFE gene testing
    - C282Y homozygote
      - Hemochromatosis
        - Phlebotomy
        - If SF is >4000 ng/mL, age >40, consider liver biopsy
    - Other HFE genotypes
      - Rule out co-morbidities
        - If abnormal iron tests persist
          - Liver biopsy
  - Non-Caucasians
    - Rule out co-morbidities
    - If abnormal iron tests persist
      - Liver biopsy

TS high, SF normal
- Caucasians and Non-Caucasians
- Consider other diagnosis

TS normal, SF high
- Caucasians and Non-Caucasians
- Rule out causes of high SF (e.g., alcohol, cell necrosis, metabolic disorders, inflammation, cancer)
  - If none of the above or high SF persists after their management, perform MRI or liver biopsy

Iron overload
- Consider ferroportin disease (particularly if Kupffer cell iron deposits)
- FPN gene sequencing
  - Pathogenic mutation
  - Ferroportin disease

No iron overload
- Consider other diagnosis

HC pattern of iron overload
- In HFE Wt/WT
  - In HFE C282Y/WT or H63D/WT
  - In HFE C282Y/H63D or H63D/H63D

Non-HC pattern of iron overload
- Tfr2-FPN gene sequencing
  - Pathogenic mutation
  - Hemochromatosis
  - Phlebotomy

If SF is >4000 ng/mL, age >40, consider liver biopsy
Recommendations for Genetic testing

EASL guidelines – J. hepatol 2010;53:3-22

• General population
  – Unexplained chronic liver disease with high TS
  – Pts with Porphyria CT, well-defined chondrocalcinosis, HCC
  – Type 1 DM

• Suspected iron overload: fasting SF and TS
  – HFE genotyping only if TS elevated (at least once)
  – Testing for C282Y and H63D polymorphism

• Consider liver biopsy if ferritin > 1000 µg/L
Ferritin: a prognostic marker

- SF: predictor of risk of cirrhosis
- Multiples studies:
  - Cirrhosis rarely occurs if ferritin < 1000 µg/L
- Allows estimation of incidence of cirrhosis in C282Y homozygous patients
  - Liver Bx in 350/672 pts (SF > 500 µg/L, hepatomegaly, elevated TA)
  - Cirrhosis: 5.6% of males, 1.9% of females (all ferritin > 1000 µg/L)
  - ROC curve Ferritin 1653 µg/L
    - Se 90%, Sp 92 % for predicting cirrhosis

Ferritin: monitor of treatment

• SF sufficient to monitor iron depletion
• Endpoint of therapeutic phlebotomy (standard of practice)
  – SF < 20-50 µg/L, TS < 30 % (within 1-2 yrs)
• Maintenance (prevent re-accumulation)
  – Keep SF between 50-100 µg/L
• Other approach
  – Resume phlebotomy when SF reaches upper limit of normal
Ferritin: predictor of steatosis in chronic liver diseases

• 124 patients with hyperferritinemia
• Steatosis confirmed by U/S (present or absent)
• Histology in 53 pts only
• 43% hep C, 46% NAFLD/NASH, 11% AFLD
• Ferritin: independent predictor of steatosis (in non-obese non alcoholic patients)
• High SF associated with more advanced disease (low platelets, portal hypertension)

Radicheva M. Trakia J Sci 2010
Ferritin and OLT

• Hypothesis: elevated SF important predictor of mortality in patients awaiting OLT, independently of MELD
• Retrospective analysis
• 191 patients with cirrhosis
• 2000-2006

Walker N. Hepatology 2010
- SF important and independent factor in predicting 180 d and 1 year mortality
- Identified both in study and validation cohort
- Higher frequency of liver related complications during follow-up in patients with high SF (necro-inflammatory activity)
AUC for MELD vs. MELD+SF

Fig. 2. ROC curve of MELD and MELD plus SF as predictors of mortality at 180 days.

Fig. 3. ROC curve of MELD and MELD plus SF as predictors of mortality at 1 year.
Ferritin in evaluation of anemia by colonoscopy

Conclusion: Ferritin value of 100 µg/L should be used as cut-off for selecting patients with anemia for colonoscopy

Mandeep S. Am J Gastro 2007:102:82-88