Hereditary Hemochromatosis
Making the Diagnosis in Primary Care

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Topics to be Discussed

- Epidemiology of hemochromatosis
- Clinical Manifestations, Diagnosis and Differential Diagnosis of Hemochromatosis
- Appropriate use of genetic testing
- Treatment
- When to refer to the specialist
- Take-home points
Definition and Epidemiology of Hemochromatosis

- Autosomal recessive disorder resulting in increased intestinal absorption of iron
- Incidence of about 5 to 10 per 1000 patients of Caucasian descent
- Most have mutations of the HFE gene
- It needs to be distinguished from other causes of iron overload
Types of Hemochromatosis

- Type I HFE
- Type 2 juvenile hemochromatosis
  - Hemojuvelin and hepcidin mutations
- Type 3 transferrin receptor II mutations
- Type 4 ferroportin mutations
Clinical Manifestations

- Liver function abnormalities — 75 percent
- Weakness and lethargy — 74 percent
- Skin hyperpigmentation — 70 percent
- Diabetes mellitus — 48 percent
- Arthralgia — 44 percent
- Impotence in males — 45 percent
- Electrocardiographic abnormalities — 31 percent.
Clinical Manifestations-continued

- However note that the majority of patients are asymptomatic at the time of diagnosis
  - Family screening
  - Ferritin and iron saturation were ordered for another reason

- Note that HH patients have an at least 20-fold increased risk of hepatocellular carcinoma
Diagnosis of Hemochromatosis

- **Biochemistry tests**
  - Ferritin - greater than 1000 ug/L
  - Fasting Iron/TIBC ratio
    - Greater than 60 percent in males and 50 percent in females

- **Genetic testing (Caucasian Descent Type I)**
  - C282Y/C282Y (cysteine to tyrosine)
  - C282Y/H63D (histidine to aspartic acid)
Diagnosis of Hemochromatosis- continued

- Liver MRI/liver biopsy- to quantify hepatic iron overload
  - Rare that liver biopsy is necessary unless there is suspicion of end-stage cirrhosis
Differential Diagnosis of Hemochromatosis

- Transfusion iron overload
- Hematologic disorders
  - Ineffective erythropoiesis
- Elevated ferritin without iron overload
  - Acute phase reactant related to inflammation
  - Benign
- Rare genetic syndromes
  - Aceruloplasminemia, neuroferritinopathy
Appropriate Use of Genetic Testing

- Patient of Caucasian descent with serum ferritin of greater than 500 ug/L and a fasting transferrin saturation of at least 50 percent
- First-degree relative of an index patient with a documented C282Y/C282Y or C282Y/H63D
- Note that a negative genetic test does not definitively rule out HH
Treatment

■ Most patients are asymptomatic but treatment is indicated to prevent sequelae if ferritin is greater than 500 ug/L

■ Phlebotomy (usually weekly) to decrease the serum ferritin to less than 50 ug/L

■ Once obtained less frequent phlebotomy is necessary to maintain this level

■ If phlebotomy contraindicated: iron chelating agents
When to Refer to the Specialist

- All patients with an elevated serum ferritin level should have an iron saturation done.
- If iron saturation is normal there is no need for hematologist referral.
- If patient meets criteria for genetic testing then it should be done prior to referral.
When to Refer to the Specialist—continued

- If there is a question about the diagnosis or management refer to a specialist but the initial workup should be completed first.

- Also refer to a specialist if there is suspected end-organ damage.

- Phlebotomy does not have to be done by the specialist but many clinics/treatment areas are not set up to do it so referral may be necessary.
Take-Home Points

- HH is more common than we thought and most patients are asymptomatic at the time of diagnosis.
- Elevated ferritin and iron saturation confirm the presence of iron overload but other causes of iron overload need to be ruled out.
- Genetic testing can be helpful to confirm type I HH but negative testing does not rule out the diagnosis.