Hemochromatosis

Definition

- Common disorder of iron storage
- Inappropriate increase in intestinal iron absorption
- Deposition of excessive iron in parenchymal cells with tissue damage
- Liver, pancreas, heart, joints, and pituitary
- Potentially severe progressive iron overload leading to fibrosis and organ failure

Definition

- Common manifestations include liver cirrhosis, DM, arthritis, cardiomyopathy, and hypogonadotrophic hypogonadism
- Genetic or hereditary vs secondary iron overload

Prevalence

- Common in northern Europeans- 1 in 10 are heterozygotes
- Expression of disease is modified by dietary iron intake, blood loss, and blood donation
- Clinical expression 5-10 times more frequent in men
- 70% develop symptoms between 40-60 y/o

Genetic Basis

- Gene involved in most common form is HFE, causing cysteine→tyrosine
- Autosomal recessive
- Mutations in other genes responsible for other types including juvenile hemochromatosis

Pathogenesis

- Normal iron content is 3-4g
- Absorption equals loss: 1mg/d in men, 1.5mg/d menstruating women
- Hemochromatosis: absorb 4mg/d+
- Early elevation in plasma iron, increased transferrin sat, progressive elevation of ferritin
- The mutated gene causes an upregulation of the iron transport mechanism on the brush border cells

Pathogenesis- Secondary Iron Overload

- Deposition occurs in chronic disorders of erythropoiesis
  - Defects in hemoglobin synthesis
  - Ineffective erythropoiesis- sideroblastic, thalassemia
- Absorption of iron is increased
- Compounded by blood transfusions

Pathogenesis- Secondary Iron Overload

- Alcoholics with CLD may have iron stores to this degree- caused by cell death and released iron and hemolysis of spur cells
- Excessive iron ingestion over many years rare cause
- Pts with parenteral iron or blood transfusions have reticuloendothelial cell iron overload, not parenchymal cell/ tissue damage

Pathology

- Enlarged rusty nodular liver and pancreas
- Thin skin with increased melanin in basal layer of epidermis
- Iron deposits present around synovial lining cells of joints
- Liver- macro or mixed macro/micronodular cirrhosis develops

Clinical manifestations

- Nonspecific initial symptoms
  - Weakness, wt loss, change in skin color
  - abdominal pain, loss of libido, DM symptoms
- Advanced disease: Hepatomegally , increased pigmentation, spider angiomas, splenomegaly, arthropathy, ascites, cardiac arrhythmias, CHF, loss of body hair , testicular atrophy, jaundice

Clinical manifestations

- Liver usually first affected- HM in 95%
- Hepatocellular Ca develops in 30% with cirrhosis- most common cause of death in treated pts
- Skin hyperpigmentation- 90%- increased melanin and iron in dermis
- DM in 65%

Clinical manifestations

- Arthropathy in 25-50%
  - 2nd & 3rd MCP first
  - Progressive polyarthropathy
  - Not improved by phlebotomy
- Cardiac- 15%- CHF, arrhythmias
- Hypogonadism- decreased production of gonadotropins due to impairment of hypothalamic-pituitary function by iron deposition

Diagnosis

- High clinical suspicion
- History- fam hx, alcohol ingestion, iron intake, ascorbic acid intake
- Exclude hematologic disease
- Confirm presence of liver, pancreatic, cardiac, and joint disease

Diagnosis

- Assess parenchymal iron stores:
  - 1 Iron and transferrin sat
  - 2 ferritin
  - 3 liver biopsy
  - 4 Estimate chelatable iron stores after deferoxamine
  - 5 CT/MRI

Diagnosis

- Fasting transferrin sat >50% suggests homozygosity
- Ferritin is good index of iron stores
- Combined transferrin sat and ferritin is a simple and reliable screening test
- Role of liver biopsy being reassessed in light of readily available genetic testing

Treatment

- Removal of excess body iron and support for damaged organs
- Phlebotomy 1-2 x weekly, 500cc each
- Ferritin falls progressively
- Transferrin sat stays high until stores are depleted
- Phlebotomy required for 1-2 years
  - Each 500cc contains 200-250 mg iron
  - About 25 g needs to be removed
- Deferoxamine (chelating agent) removes 10-20 mg/d

Prognosis

- Causes of death
  - Cardiac failure 30%
  - Hepatocellular failure/portal HTN 25%
  - HCC 30%
- Life expectancy improved by tx/ maintenance therapy
- Hypogonadism and arthropathy not improved
- Family screening and early therapy very important

Table 345-1 Classification of Iron Overload States

Hereditary hemochromatosis
- Hemochromatosis, *HFE*-related
  - C282Y homozygosity
  - C282Y/H63D compound heterozygosity
- Hemochromatosis non-*HFE*-related
- Juvenile hemochromatosis
- Autosomal dominant hemochromatosis (Solomon Islands)

Acquired iron overload
- Iron-loading anemias
  - Thalassemia major
  - Sideroblastic anemia
  - Chronic hemolytic anemias
  - Transfusional and parenteral iron overload
- Dietary iron overload
- Chronic liver disease
  - Hepatitis C
  - Alcoholic cirrhosis, especially when advanced
  - Nonalcoholic steatohepatitis
  - Porphyria cutanea tarda
  - Dysmetabolic iron overload syndrome
  - Post portacaval shunting

Miscellaneous
- Iron overload in sub-Sahara Africa
- Neonatal iron overload
- Aceruloplasminemia
- Congenital atransferrinemia

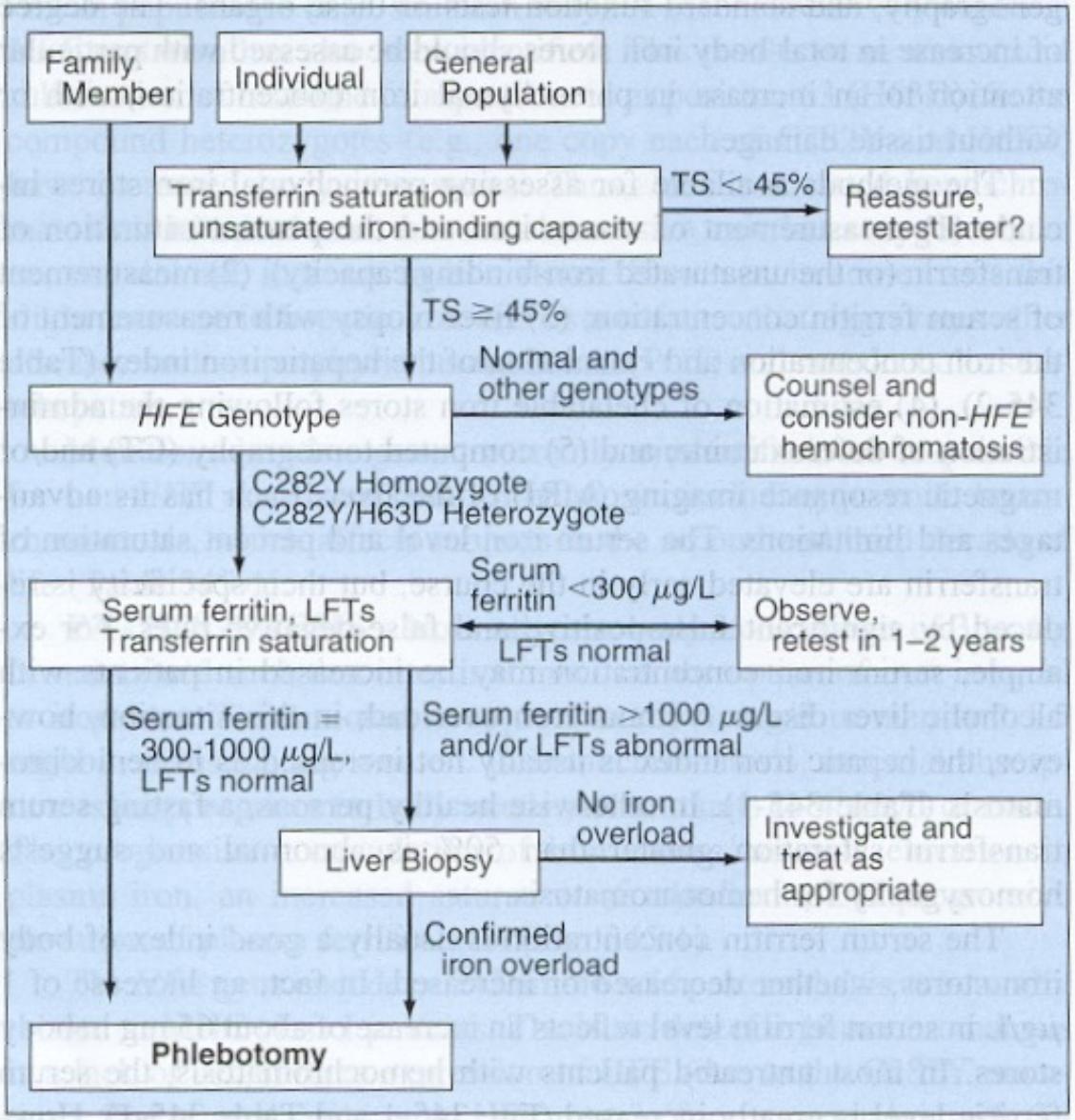

FIGURE 345-2 Algorithm for screening for *HFE*-associated hemochromatosis. LFT, liver function tests; TS, transferrin saturation. (*With permission from The Canadian Journal of Gastroenterology.*)