Hemosiderin

Livia Vida 2018

Questions

- Histochemical caracteristics of the different pigments. Exogenous pigments.
- Hemoglobinogenic pigments. Causes and forms of jaundice.
- **Hemoglobinogenic pigments. Pathological forms of iron storage.**
- Endogenous non-hemoglobinogenic pigments: lipofuscin, melanin, homogentizic acid.

Hemosiderin

Hemosiderin is a hemoglobin-derived granular pigment that is golden yellow to brown and accumulates in tissues when there is a local or systemic excess of iron.

Iron is normally stored within cells in association with the protein apoferritin, forming ferritin micelles.

Hemosiderin pigment represents large aggregates of these ferritin micelles, the iron can be identified by the Prussian blue histochemical reaction.

Although hemosiderin accumulation is usually pathologic, small amounts of this pigment are normal in the mononuclear phagocytes of the bone marrow, spleen.

Excessive deposition of hemosiderin, called hemosiderosis, and more extensive accumulations of iron seen in hereditary hemochromatosis

Non stainable iron

- Note that ferrous iron in heme groups (hemoglobin, myoglobin, cytochromes) does not stain. Neither does the ferric iron stored as ferritin, since the apoferritin protein shields the iron atoms.

Generalized Hemosiderosis

Too much iron in the whole body:

many red cell transfusions without blood loss
(i.e., diseases that ruin red cell precursors)

problems using the iron:

- ineffective erythropoiesis (thalassemia, myelodysplasia)
- "sideroblastic" anemia

Transfusion blood red cells live shorter, repeated transfusions are necessary. Iron is accumulating with every transfusion.

Local hemosiderosis

Localized hemosiderosis
Local excesses of iron and hemosiderin
result from:
1. **gross hemorrhages** - bruise
Hemoglobin: blue
Biliverdin: green
Bilirubin: red
Hemosiderin: golden yellow
2. **minute hemorrhages** due to vascular congestion
lung: induratio brunea pumonis
Liver: hepar moschatum
spleen: fibroadenia**/** Fibrosiderotic plaques
Skin: lower extremities: venous congestion

Brown induration of the lung

Due chronic left-sided heart failure severe congestion occurs.

We see “heart failure cells”, ie alveolar macrophages with hemosiderin granules (appear as brown cytoplasmic granules with H&E staining).

Note, when phagocytosed erythrocytes are broken down in macrophages the iron is removed and is bound to stored as hemosiderin granules.

Long standing congestion in the lung will lead to fibroblast activation and pulmonary fibrosis.

Induration is due to fibrosis

Brunea: due to hemosiderosis

Hemochromatosis

- Hereditary hemochromatosis refers to a genetic disorder characterized by excessive accumulation of body iron, most of which is deposited in the liver, pancreas, and heart.
- At least four genetic variants of hereditary hemochromatosis are recognized. The most common form is an autosomal recessive disease of adult onset caused by mutations in the HFE gene.
- The total body iron pool ranges from 2 to 6 gm in normal adults.
- 0.5 gm is stored in the liver in hepatocytes.
- In hereditary hemochromatosis, iron accumulates over the lifetime of the affected person from excessive intestinal absorption.
- Total iron accumulation may exceed 50 gm, over one third of which is found in the liver.
- Fully developed cases show (1) cirrhosis, (2) diabetes mellitus, and (3) skin pigmentation.

Pathogenesis

- The total body content of iron is tightly regulated.
- There is no excretory pathway for excess absorbed iron.
- In hereditary hemochromatosis there is a defect in the regulation of intestinal absorption of dietary iron, leading to net iron accumulation of 0.5 to 1.0 g/year.
- The hereditary hemochromatosis gene, responsible for the most common form of this disorder, is called *HFE*.
- Expression of the mutated HFE protein leads to upregulated absorption of iron.
- Hepcidin is the iron hormone produced by the liver. Hepcidin normally down-regulates the efflux of iron from the intestines and inhibits iron absorption. When hepcidin levels are reduced there is increased iron absorption.
- Hepcidin levels are reduced in hemochromatosis.

Pathogenesis

Hereditary hemochromatosis manifests typically after 20 gm of storage iron has accumulated.

Regardless of source, excessive iron seems to be directly toxic to tissues by the following mechanisms:

- Lipid peroxidation, protein oxidation by iron-catalyzed free radical reactions
- Stimulation of collagen formation= fibrosis=scar tissue
- Direct interactions of iron with DNA

Morphology

The morphologic changes in hereditary hemochromatosis are all responses to the **deposition of hemosiderin** in the following organs (in decreasing order of severity):

- liver
- pancreas
- myocardium
- pituitary
- adrenal
- thyroid and parathyroid glands
- joints and skin

In the liver, iron becomes evident as golden-yellow hemosiderin granules in the cytoplasm of periportal hepatocytes and Kupffer cells. Iron is a direct hepatotoxin.
The liver typically is larger than normal (hepatomegaly), dense, and brown. Fibrous septa develop slowly, leading ultimately to **cirrhosis** in an intensely pigmented (very dark brown) liver.

Morphology

The **pancreas** becomes intensely pigmented, acquires fibrosis, and shows parenchymal atrophy. Hemosiderin is found in the acinar and the islet cells.

The **heart** often is enlarged, with hemosiderin granules within the myocardial fibers.

Although **skin** pigmentation is partially attributable to hemosiderin deposition most of the coloration results from increased epidermal melanin production.

With hemosiderin deposition in the **joint synovial linings,** an acute synovitis, polyarthritis develops.

The **testes** and **ovaries** are smaller (atrophic) as well as all the other endocrine organs, endocrine pancreas included.

Clinical features

- Symptoms usually first appear in the fifth and sixth decades of life. Males predominate.
- The principal manifestations include hepatomegaly, skin pigmentation, diabetes mellitus from destruction of pancreatic islets, cardiac dysfunction (arrhythmias, cardiomyopathy), and arthritis.
- The classic clinical triad of cirrhosis with hepatomegaly, skin pigmentation, and diabetes mellitus develop late in the course of the disease.
- The risk for hepatocellular carcinoma development in patients with hemochromatosis is 200 times higher than in normal populations.

Hereditary hemochromatosis can be diagnosed long before irreversible tissue damage has occurred.

Importance of screening

Screening involves demonstration of very high levels of serum iron and ferritin, exclusion of secondary causes of iron overload, and liver biopsy if indicated.

Also important is screening of relatives.

The natural course of the disease can be substantially altered by phlebotomy and the use of iron chelators (Desferal®)to decrease total body iron.

Patients diagnosed in the subclinical, precirrhotic stage and treated by regular phlebotomy have a **normal life expectancy**.

Heterozygotes may show a mild increase in iron absorption and accumulation.