Bilirubin and hemosiderin deposits
Pigments

- Definition
- Classification
- Blood pigment breakdown
  - extravascular
  - intravascular
- Hemosiderin
  - location
  - complications
- Hemochromatosis
- Icterus
  - definition
  - types
  - complications
Pigments

Definition:

colored substances in the organism or environment
Pigments

**Classification:**

- **endogenous**
  - hemoproteins
  - autogenous
- **exogenous**
Hemoproteins Derived Pigments

- colour substances originating from *hemoglobin* modification or breakdown
Iron metabolism

- Daily iron need on average 1mg
- Losses: bile, sweat ....
- Turnover regulated by the HEPcidin & FERROportin
**Hepcidin** (& Ferroportin)

- a 25-amino acid peptide hormone
- synthesized in the liver
- secreted in plasma
- binds to the cellular iron export channel ferroportin causing its internalization and degradation, thereby
- *decreasing iron efflux* from iron exporting enterocytes and macrophages into plasma

**CENTRAL REGULATOR OF BODY IRON METABOLISM**
Ferroportin

- a transmembrane protein that transports iron from the inside of a cell to the outside of it.

- found on the surface of cells that store or transport iron, including:
  - Enterocytes in the duodenum
  - Hepatocytes
  - Macrophages of the reticuloendothelial system.
Hepcidin (H) – Ferroportin (F) pathology conditions:
A. chronic inflammation – high H levels, F degradation, macrophage iron loading, transferrin saturation & haemopoetry, anemia
B. NORM
C. hemochromatosis – low H levels, high transferrin saturation, excess iron deposition in the liver

Accumulation of Intracellular Iron in Alzheimer’s disease

(ferroportin disabled)

APP helps to secure ferroportin (Fpn) on the cell surface. Ferroportin is the only known channel to transport iron (Fe) out of the cell.

In Alzheimer’s disease, APP is removed from the system by being cut up to form β-amyloid peptide.

Without APP securing ferroportin, levels of ferroportin drop on the cell surface. This in turn leads to a toxic build up of iron in the cell.
Hemoproteins Derived Pigments

- oxyhemoglobin \((\text{Fe}^{2+})\)
- hematin \((\text{Fe}^{3+})\)
- methemoglobin (globin + hematin)
- carboxy/ carbonyl/ hemoglobin
Complexus varicosus crurum
Carboxyhemoglobin - carbon monoxide poisoning
Blood Pigment Breakdown

- extravascular
- intravascular
Extravascular Blood Pigment Breakdown

Hemoglobin $\rightarrow$ heme oxygenase

$\rightarrow$ biliverdin $\rightarrow$ biliverdin reductase

$\rightarrow$ bilirubin (cells of MPS) + globin + Fe
fresh bruise

old bruise
Extravascular Blood Pigment Breakdown

Globin $\rightarrow$ aminoacids

$Fe \rightarrow$ hemosiderin

$Fe(OH)_3 +$ protein carrier

hematoidin = tissue bilirubin

(+ceroid)

Etymology: Gk: haima blood + sideros, iron
Hemosiderin - Features

- brown
- forms a deep blue product

**Prussian blue** with acid potassium ferocyanide solution $K_4[Fe(CN)_6].3H_2O$

*Perls’ reaction*
bilirubin and hemosiderin deposits
Congestion of the Lungs

Hyperemia
Acute

Beginning induration
Subacute

Chronic congestion
(Stasis) of lung

Fig. 106. Different stages of congestion of the lung.
Venostasis pulmonum chronica – induratio rubra
Venostasis pulmonum chronica – induratio rubra
Pseudocystes posthaemorrhagicae cerebri
Sputum - hemosiderophages
Hemochromatosis

- **Autosomal Recessive** \((M:F = 5:1)\)
  - 6th chromosome – mutations
  - hepcidin/ferroportin insufficiency
  - prevalence 0.3–0.8 % (!!!)
- **deblocation of Iron intake**
  - (Iron need = cca 1–2mg/day)
- **deposits of HEMOSIDERIN:**
  - pancreas & skin (diabetes bronze), myocardium, pituitary, joints, liver

**PHLEBOTOMY THERAPY**

Mutations in
- HFE (= High Fe in the serum) gene
- transferrin receptor 2
- hemojuvelin
- hepcidin gene itself
Hepcidin (H) – Ferroportin (F) pathology conditions:

A. chronic inflammation – high H levels, F degradation, macrophage iron loading, transferrin saturation & haemopoetry, anemia

B. NORM

C. hemochromatosis – low H levels, high transferrin saturation, excess iron deposition in the liver

Hemochromatosis – liver cirrhosis
Haemochromatosis – liver, pancreas, lymph node
Hemochromatosis – cirrhosis hepatis
Pancreas - haemochromatosis
Haemochromatosis myocardii

Fe
Hemochromatosis - life threatening complications

- cirrhosis
- hepatocellular carcinoma
- heart failure
- arrhythmia
- diabetes
Blood Pigment Breakdown

- extravascular
- intravascular
Intravascular Blood Pigment Breakdown

Hemoglobin → bound to haptoglobin (α₂-globulin) + Fe

biliverdin
bilirubin
urobilinogen
stercobilinogen
urobilin
stercobilin

enterohepatal circulation

norm in blood: 1,7-17,4umol/l
Nephrosis vasoparalytica
Haemosiderosis hepatis
Haemosiderosis hepatis
Bilirubin Processing

- transport to the liver
- hepatocyte entry – hepatocyte blood pole
- glucuronylation
- output to bile - hepatocyte bile pole
Icterus – Jaundice

Definition:

a condition (symptom!) in which the tissues are yellowish due to the increase of bilirubin concentration

(normal plasma: 1,7-17,4 umol/l unconj. bilirubin bound to albumin)
Icterus cutis, sclerarum, mucosae
Icterus obstructivus

Cachexia
Bilirubin Processing

- transport to the liver
- hepatocyte entry – hepatocyte blood pole
- glucuronylation
- output to bile - hepatocyte bile pole
Icterus – Jaundice

- **generalized**
  - prehepatal
    - flavin
  - hepatal
    - ruby
  - posthepatal
    - verdant
    - icterus
    - melas

- **local**
  - surrounding hematoma
Icterus cutis et sclerarum
Icterus

- hemolytically (dynamic)
- hepatocellular (dissociated)
- obstructive (resorptive)
- MIXED
Icterus

- hemolytical (dynamic)
  - corpuscular:
    - hered. spherocytosis, defect of G6P-dehydrogenase)
    - hemoglobinopathies
      - sickle cell anemia glu-val
      - thalassaemiae – tetramers a- globin or b – globin
      - ...
  
- extracorpuscular
  - icterus neonati simplex
  - icterus neonati gravis…
Hemolytic Disease of the Newborn
Morbus hemolyticus neonati –
erthroblastosis fetalis

- Rh- mother with an Rh+ fetus
- anti Rh IgG crossing the placenta barrier
  - anaemia neonati
  - icterus neonati gravis
  - hydrops fetus universalis
  - abortus
Morbus haemolyticus neonati. Hydrops fetus universalis. Fetus maceratus.
Morbus haemolyticus neonati
hydrops fetus universalis
Morbus haemolyticus neonati.
Kernicterus
Ceroid & Lipofuscin

**Origin** - the basic mechanisms of formation are the same:

– auto- or heterophagocytosis of modified lipid substances (membranes, mitochondriae) in lysosomes

– oxidation of non-saturated lipid acids

**Lipofuscin** – slowly within postmitotic cells

**Ceroid** – transient, during any period of life in any tissue
Features

Ceroid
- light brown
- PAS +
- acidoresistent
- Sudan +-.

Lipofuscin
- dark brown
- PAS +
- acidoresistent
- Sudan +-.

AUTOLUMINESCEENCE
Ceroid

- localisation
  - places of erythrocytes destruction
  - necroses of adipose tissue
  - avitaminosis E
  - melanosis coli
  - Dubin - Johnson syndrome
Icterus

- **hepatocellular (dissociated)**
  - hepatotoxic – acquired
    - CCl₄, amanitin,
    - hepatitis epidemica, febris flava,
    - leptospirosis, bact. sepsis...
  - enzymopathies – inborn
    - Crigler–Najjar
    - Gilbert - glucuronyltransferase defect
    - Dubin–Johnson, Rotor
Icterus

- posthepatal – obstructive
  - acquired
    - obstruction
      - intraluminal
      - intramural
      - extramural
  - inborn
    (primary billiary atresia)
Blockage of the Biliary Ways - causes

- multiple intrahepatal
- both right and left hepatic ducts
- common hepatic duct
- choledochus
- papilla Vateri

- intraluminal - stone, ascaris...
- intramural - non-neoplastic (inflamm.), neoplastic...
- extramural – non-neoplastic, neoplastic
- combined
cholecysto- et choledocholithiasis
Blockage of the Biliary Ways

- complications

- icterus
- cholalaemia
- cholangiogenic sepsis
- biliary cirrhosis
- bleeding disorders
Cholestasis hepatis
Cholestasis hepatis
Cholestasis hepatis
Cholelithiasis vesicae felleae
Cholelithiasis. Empyema vesicae felleae chronicum.
Nephrosis cholaemica
Nephrosis cholaemica
Nephrosis cholaemica
Cirrhosis biliaris hepatis
Icterus

- *hemolytical (dynamic)*
- *hepatocellular (dissociated)*
- *obstructive (resorptive)*
- *MIXED*
## Table of diagnostic tests

<table>
<thead>
<tr>
<th>Function test</th>
<th>Pre-hepatic Jaundice</th>
<th>Hepatic Jaundice</th>
<th>Post-hepatic Jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>Normal / Increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Conjugated bilirubin</td>
<td>Normal</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Normal / Increased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>Normal / Increased</td>
<td>Decreased</td>
<td>Decreased / Negative</td>
</tr>
<tr>
<td>Urine Color</td>
<td>Normal</td>
<td>Dark (urobilinogen + conjugated bilirubin)</td>
<td>Dark (conjugated bilirubin)</td>
</tr>
<tr>
<td>Stool Color</td>
<td>Normal</td>
<td>Normal/Pale</td>
<td>Pale</td>
</tr>
<tr>
<td>Alkaline phosphatase levels</td>
<td>Normal</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Alanine transferase and Aspartate transferase levels</td>
<td>Normal</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Conjugated Bilirubin in Urine</td>
<td>Not Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>