HEMOCROMATOSIS HEREDITARIA Y OTRAS SOBRECARGAS DE HIERRO

HIERRO E HÍGADO

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Il Curso de Hepatología Clínica y lo mejor de ALEH / AASLD / APASL / EASL
* Northern European descent
**Hereditary hemochromatosis (E)s**

- HH is an inherited predisposition to absorb excess iron (Fe) from the diet.
- Mutations in the *HFE* gene are the most common cause of adult onset iron overload.
- In some predisposed individuals, excessive iron absorption and subsequent storage in various organs (i.e. liver, pancreas, heart, joints) eventually lead to cellular injury.
- If untreated, over time this can cause irreversible tissue/organ damage and shorten life expectancy.
- With early identification of at-risk individuals, surveillance of iron indices, and treatment when necessary, **all complications can be avoided**.
- Other causes of iron overload need to be explored.
Iron metabolism

Daily Diet contains 10-20 mg iron

Absorb 1-2 mg iron/day

TRANSFERRIN (transports iron)

Lose 1-2 mg iron/day from desquamation of epithelia

75%

10-20%

5-15%

Hemoglobin/Erythropoiesis

FERRITIN (stores iron in liver & heart)

No Physiologic Excretion Mechanism

Other Processes
Hemochromatosis: physiopathology
The four players

Iron Cycle

Enterocyte

Erythroid precursor

Macrophage

Hepatocyte
Iron $\text{Fe}^{3+}$ is reduced to ferrous $\text{Fe}^{2+}$ by the duodenal cytochrome B reductase and imported into the cytoplasm by the divalent metal transporter 1 (DMT1), which is expressed in the apical membrane of the enterocytes.

Intestinal expression of iron transporter DMT1 (SLC11A2) is regulated by transcriptional and post-transcriptional mechanisms upon intracellular iron status.

Once within the cell, iron is either stored in the form of ferritin or is transported to the iron exporter ferroportin (FPN) located in the basolateral membrane of the enterocyte.

FPN, which is encoded by the $\text{SLC40A1}$ gene, is the only known iron exporter in vertebrate cells.

In plasma, $\text{Fe}^{2+}$ is oxidized to $\text{Fe}^{3+}$ by ferroxidases (hephaestin and ceruloplasmin) and then carried by transferrin.

The main regulator of expression of ferroportin is hepcidin.
The link-central regulator: hepcidin

Iron-sensing complex: BMP=bone morphogenetic protein receptors (BMPRs), hemojuvelin (HJV), transferrin receptor 2 (tFR2), and HFE protein
The net effect on iron stores probably reflects the counterbalance between genetic, disease-associated, and patient-related factors.
## HH types

### HFE-related HH

- **Classic hemochromatosis**
  - **affected gene**: HFE
  - **mutations**: > 30 different mutations most frequent:
    - HFEC282Y
    - HFEH63D
    - HFE S65C
  - **molecular consequences**: low hepcidin levels, tissue iron overload
  - **symptoms**: mild to severe

### Non-HFE-related HH

- **A + B**
  - **affected genes**: HJV (HFE2) (type II A) or HAMP (type II B)
  - **mutations**: HJV
    - > 30 different HJV mutations
      - most frequent: HJV p.G320V
  - **molecular consequences**: low hepcidin levels, tissue iron overload
  - **symptoms**: severe, at young age

- **Juvenile HH**
  - **affected genes**: HAMP
  - **mutations**: 13 different HAMP mutations
  - **molecular consequences**: low hepcidin levels, tissue iron overload
  - **symptoms**: severe, at young age

### TfR2-related HH

- **Classical FD with loss-of-function mutations**
  - **affected gene**: FPN (SLC40A1)
  - **mutations**: e.g. FPN Y64N, V72F
  - **molecular consequences**: loss of FPN function, iron overload in macrophages (Liver + spleen)
  - **symptoms**: generally none

- **Classical FD with gain-of-function mutations**
  - **affected gene**: FPN (SLC40A1)
  - **mutations**: e.g. FPN D157N, D181V
  - **molecular consequences**: gain of FPN function, hepcidin resistance, tissue iron overload
  - **symptoms**: mild to severe

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*Hollerer I et al, *Haematologica* 2017; Volume 102(5):809-817*
### Hereditary iron overload disorders with hyperferritinemia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Responsible gene and inheritance</th>
<th>TSAT</th>
<th>Serum hepcidin</th>
<th>Anemia</th>
<th>Neurologic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH type 1</td>
<td><em>HFE, AR</em></td>
<td>High</td>
<td>Low</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HH type 2a</td>
<td><em>HJV (HFE2), AR</em></td>
<td>High</td>
<td>Low</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HH type 2b</td>
<td><em>HAMP, AR</em></td>
<td>High</td>
<td>Absent</td>
<td>–</td>
<td>–</td>
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<tr>
<td>HH type 3</td>
<td><em>TFR2, AR</em></td>
<td>High</td>
<td>Low</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HH type 4A</td>
<td><em>SLC40A1, AD</em></td>
<td>Normal</td>
<td>High</td>
<td>Variable</td>
<td>–</td>
</tr>
<tr>
<td>HH type 4B</td>
<td><em>SLC40A1, AD</em></td>
<td>High</td>
<td>High</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thalassemia</td>
<td><em>HBB, AR</em></td>
<td>High</td>
<td>Low</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td><em>HBA, AR</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDA</td>
<td><em>CDAN1, AR</em></td>
<td>High</td>
<td>Low</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td><em>SEC23B, AR</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><em>KIF23, AD</em></td>
<td></td>
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<tr>
<td>CSA</td>
<td><em>ALAS2, XL</em></td>
<td>High</td>
<td>Low</td>
<td>+</td>
<td>ALAS2, –</td>
</tr>
<tr>
<td></td>
<td><em>SLC25A38, AR</em></td>
<td></td>
<td></td>
<td></td>
<td>SLC25A38, –</td>
</tr>
<tr>
<td></td>
<td><em>GLRX5, AR</em></td>
<td></td>
<td></td>
<td></td>
<td>GLRX5, +</td>
</tr>
<tr>
<td></td>
<td><em>ABCB7, XL</em></td>
<td></td>
<td></td>
<td></td>
<td>ABCB7, +</td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
<td><em>CP, AR</em></td>
<td>Low</td>
<td>Low</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atransferrinemia</td>
<td><em>TF, AR</em></td>
<td>High</td>
<td>Low</td>
<td>+</td>
<td>–</td>
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<tr>
<td>HX/DHS</td>
<td><em>PIEZO1, AD</em></td>
<td>High</td>
<td>Low</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

While any of these health concerns can be caused by HH, the presence of two or more should greatly increase suspicion that the condition is present.
It’s a spectrum of disease

- Phenotypic expression only occurs in about 70% of C282Y homozygotes
- Less than 10% of C282Y homozygotes will develop severe clinical manifestations secondary to iron overload

Stage 1: Genetic susceptibility = Genetic disorder +, no increase in iron stores

Stage 2: Genetic disorder, phenotypic evidence of iron overload without tissue or organ damage

Stage 3: Genetic disorder, iron overload WITH tissue & organ damage
Natural progression of disease

- Cirrhosis, organ failure
- Progressive tissue injury
- Increased total body iron
- Increased hepatic iron
- Increased serum iron
- Increased iron absorption
Outcome

- Early diagnosis
- Screening & early detection of **asymptomatic HH**
- Recognize and diagnose **symptomatic HH**, to minimize progression and avoid complications by adequate therapy
- Maintenance therapy

**Asymptomatic**
- First degree relatives (8-30 yrs)
- **Markers of iron overload in routine blood tests**
  - Liver enzymes elevated
  - Hepatomegaly

**Symptomatic**
- Unexplained liver disease
- Liver disease with markers of iron overload
- Type II DM with hepatomegaly, increased liver enzymes, atypical cardiopathy, or gonadal dysfunction
- Arthropathy, cardiopathy or sexual dysfunction at young ages
**STEP 1**

Clinical Suspicion for HH or Elevated Liver Enzymes

**STEP 2**

Transferrin Saturation (TS) and Ferritin (SF)

- TS < 45% and Normal SF
  - Stop: Eval negative for HH

- TS ≥ 45% +/- Elevated SF
  - HFE Genotype
## Iron overload in other chronic liver diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hyperferritinemia (%)</th>
<th>Increased Transferrin saturation</th>
<th>HFE mutations (%)</th>
<th>Hepatic iron deposition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>58%</td>
<td>35-58%</td>
<td>34-48%</td>
<td>17-42%</td>
</tr>
<tr>
<td>AIH</td>
<td>65%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>25%</td>
<td>20%</td>
<td>34-48%</td>
<td>17-42%</td>
</tr>
<tr>
<td>HBE</td>
<td>415%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>63%</td>
<td>29%</td>
<td>8-16%</td>
<td>22-52%</td>
</tr>
</tbody>
</table>
Simplified algorithm for investigation and management of elevated serum ferritin levels.

- **Increased Serum Ferritin**
  - **Transferrin Saturation <50%**
    - Consider: Excess Alcohol, Metabolic Syndrome, Inflammatory States
    - Assess & Manage Appropriately
  - **Transferrin Saturation >50%**
    - **C282Y Homozygous**
      - Regular Phlebotomy
      - Fibroscan or Liver Biopsy (if abnormal LFTs or SF>1000ug/L)
      - Family Screening
      - Haemochromatosis Genetic Testing
    - **Non-HFE Hereditary Haemochromatosis** (See Table 1)
    - Venesect to normal SF and observe periodically
  - **Haemochromatosis**
    - C282Y/H63D compound heterozygote
STEP 3: CONFIRM IRON OVERLOAD
MRI: INTRAHEPATIC IRON CONCENTRATION

UNTREATED HEMOCHROMATOSIS

HH 1 YEAR FOLLOWING PHLEBOTOMIES
Who should be offered genetic testing?

- Any adult with biochemical evidence of iron overload
  - >45% transferrin saturation (TS) and >300μg/L serum ferritin (SF) in men and post-menopausal women or >200μg/L SF in pre-menopausal women
- Unexplained chronic liver disease and increased TS
- An adult with a first-degree relative (sibling, parent or child) with one of the following genetic test results:
  - C282Y/C282Y (homozygote)
  - C282Y/H63D (compound heterozygote)
  - C282Y/S65C (compound heterozygote)
  - C282Y heterozygote (carrier)
- Family history of iron overload, liver disease, type II diabetes, arthritis, heart disease (relatives with symptoms of HFE-HH)
What does the genetic test result mean?

- Two mutations identified confirm HH diagnosis in an individual with biochemical evidence of iron overload.
- Two mutations identified in an asymptomatic individual suggest risk of developing iron overload and yearly monitoring of iron indices is recommended.

<table>
<thead>
<tr>
<th>HFE mutations identified</th>
<th>Risk of iron overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y/C282Y</td>
<td>Highest risk of developing iron overload (38-50%)</td>
</tr>
<tr>
<td></td>
<td>- Many of these individuals never accumulate enough iron to cause disease</td>
</tr>
<tr>
<td></td>
<td>(about 10-33% may develop HH related symptoms)</td>
</tr>
<tr>
<td>C282Y/H63D</td>
<td>About 2% lifetime risk of developing iron overload</td>
</tr>
<tr>
<td>C282Y/S65C</td>
<td>Low lifetime risk of developing iron overload - similar to C282Y/H63D</td>
</tr>
<tr>
<td>H63D/H63D</td>
<td>About 1% lifetime risk of developing iron overload</td>
</tr>
</tbody>
</table>
Treatment: Phlebotomies

Figure 1. Algorithm for management and monitoring of phlebotomy therapy in HFE C282Y homozygous HH.
Benefits of *HFE* mutations

**Negative effects of C282Y mutations**

- **neurological system**
  - ataxia
  - depression
  - memory

- **musculoskeletal system**
  - joint pain
  - joint disease

- **cardiovascular system**
  - heart disease
  - heart failure

- **gastrointestinal tract**
  - abdominal pain
  - liver disease
  - hepatocellular carcinoma
  - hepatic myeloma

- **immune system**
  - infections due to high circulating iron levels

- **endocrine system, reproduction**
  - diabetes
  - size of male breast tissue
  - function of gonads
  - impotence
  - size of testes

- **dermatological system**
  - pigmentary changes
  - body hair

- **fitness**
  - fatigue
  - chronic fatigue
  - weakness

**Positive effects of C282Y mutations**

- **neurological system**
  - risk of developing amyotrophic lateral sclerosis (ALS), Parkinson or Alzheimer’s disease

- **cardiovascular system**
  - risk of developing atherosclerosis plaques

- **immune system**
  - intracellular iron proliferation of pathogens

- **endocrine system, reproduction**
  - [sex hormone binding] up
  - [globulin] up
  - low ferritin

- **fitness**
  - iron supply during physical activity
  - life span
  - height

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