Hereditary Hemochromatosis

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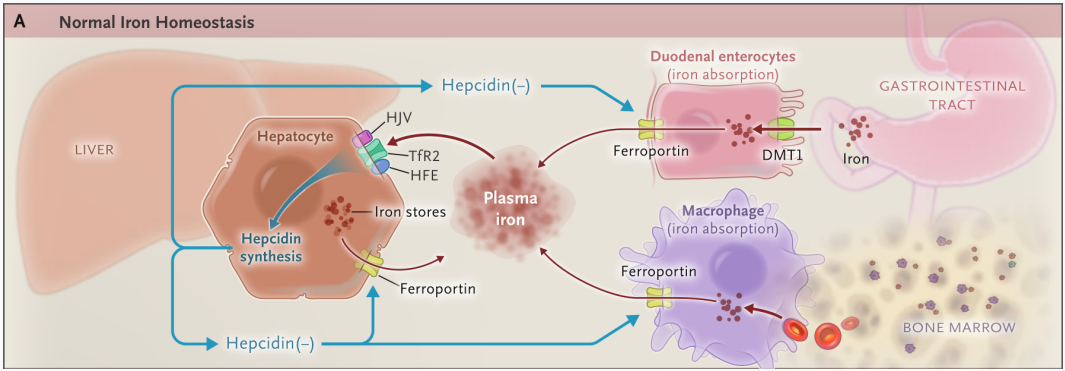
Introduction

Hereditary Hemochromatosis (HH)

- Comprises several disorders of iron homeostasis characterized by increased intestinal absorption and increased tissue deposition.

Iron homeostasis



Olynyk et al. N Engl J Med. 2022;387(23):2159–2170.

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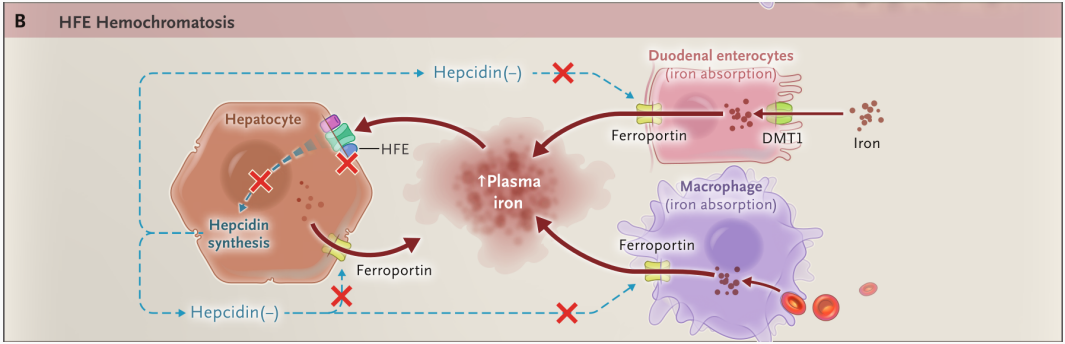

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Classification of hemochromatosis

HEREDITARY HEMOCHROMATOSIS (HH)

***HFE*-related HH (type 1)**

- C282Y homozygotes
- C282Y/H63D compound heterozygotes
- C282Y/S65C compound heterozygotes

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- Hemojuvelin (*HJV*) mutation (type 2A)
- Hepcidin (*HAMP*) mutation (type 2A)
- Transferrin receptor 2 (*TFR2*) mutation (type 3)
- Ferroportin (*SCL40A1*) mutation (type 4)
- Ferritin heavy chain 1 (*FTH1*) mutation (type 5)
- African iron overload (Bantu siderosis)

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Iron-loading Anemias

- Aplastic anemia
- Chronic hemolytic anemia
- Thalassemia major

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- Parenteral iron
- Long-term hemodialysis
- Red blood cell transfusions

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Chronic Liver Disease

- ALD, MASLD
- HBV, HCV
- Porphyria cutanea tarda

Clinical presentation

- Asymptomatic
- Fatigue
- Malaise
- Arthropathy
- Hepatomegaly
- RUQ pain
- Hypogonadotropic hypogonadism
- Cardiomyopathy
- Diabetes mellitus
- Hypothyroidism
- Bronze or slate gray skin pigmentation
- Increased risk of infection

Work-up

Iron overload

- Transferrin saturation (TS) >45%
- Ferritin
  - >300 µg/L (men, postmenopausal women)
  - >200 µg/L (premenopausal women)

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***HFE* gene mutation analysis**

- Elevated TS ± elevated ferritin
- First-degree relative with *HFE*-related HH

Work-up: *HFE* gene mutation analysis

- C282Y homozygotes
  - Biochemical penetrance: 80% (males), 50% (females)
  - Clinical penetrance: 0–30% (males), 1–12% (females)
- C282Y/H63D or C282Y/S65C compound heterozygotes
  - Very low penetrance
  - Assess for concomitant causes of iron overload

Differential diagnosis

Hyperferritinemia $\pm$ Elevated TS

- Chronic alcohol use
- Inflammation
- Cell necrosis
- Tumors
- MASLD
- Metabolic syndrome
- Secondary iron overload
- Classic ferroportin disease (type 4A)
- Aceruloplasminemia
- Hyperferritinemia-cataract syndrome
- Benign hyperferritinemia without cataracts

Work-up: assess for end-organ damage

Non-invasive tests for quantification of iron overload

- MRI: R2* sequences
- Consider in non-C282Y homozygotes
- Cardiac MRI: in juvenile HH or if evidence of cardiac involvement

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Fibrosis staging

- Biochemical and imaging-based non-invasive testing not validated for HH
- Liver biopsy if ferritin $>$1000 µ/L or if elevated AST/ALT
- Not required if diagnosis of cirrhosis is obvious

Treatment — Phlebotomy

Induction phase

- Check hemoglobin before phlebotomy
  - Hb $<$12 g/dL $\rightarrow$ reduce rate
  - Hb $<$11 g/dL $\rightarrow$ pause treatment
- Remove 500 mL of blood weekly until ferritin 50–100 µg/L
- Check ferritin every 4 phlebotomies
- Once ferritin $<$200 µg/L, check every 1–2 phlebotomies

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Maintenance phase

- Phlebotomy to maintain ferritin $<$100 µg/L (usually 2–6 phlebotomies/year)

Treatment — Other

Chelation

- Deferoxamine 20–60 mg/kg/day (SQ or IV)
  - Side effects: retinopathy, ototoxicity, neurotoxicity, opportunistic infections
- Deferiprone 75–100 mg/kg/day (oral, tid dosing)
  - Side effects: GI upset, cytopenia, agranulocytosis, arthralgias, hepatotoxicity
- Deferasirox 14 mg/kg/day (oral, daily dosing)
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Erythrocytopharesis

- Selective removal of RBC with return of platelets and clotting factors
- Can remove 1000 mL/procedure, quicker reduction in ferritin with fewer treatments

Management

Counseling

- Avoid iron and vitamin C supplementation
- Avoid daily red meat consumption and heavy alcohol use
- Avoid raw/undercooked seafood
- Avoid contact of wounds with seawater
- Screen first-degree relatives

Prognosis

- Normal life expectancy if phlebotomy started before cirrhosis and diabetes develop
- Arthropathy and hypogonadism don’t improve with phlebotomy
- Early cirrhosis may regress with phlebotomy

Management — Advanced fibrosis/cirrhosis

HCC screening

- If advanced fibrosis/cirrhosis $\rightarrow$ Ultrasound + AFP every 6 months
- CT or MRI if ultrasound suboptimal

Liver transplantation

- HH previously associated with worse post-transplant survival
- Outcomes have improved in last 20 years

Family screening

Genetic testing

- Siblings $\rightarrow$ offer genetic testing
- Children
  - Screen spouse $\rightarrow$ if *HFE* mutations absent, no need to screen children
  - Offer genetic testing in adulthood

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Biochemical screening

- Check ferritin yearly in at-risk relatives (alternative to genetic testing)

Bibliography

1. Kowdley KV, Handa P. Hemochromatosis and iron storage disorders. In: Schiff ER, Maddrey WC, Reddy KR, editors. Schiff's diseases of the liver. 12th ed. 2018. p. 820–842.
2. Pietrangelo A. Hemochromatosis. In: Sanyal AJ, Boyer TD, Lindor KD, et al, editors. Zakim and Boyer's Hepatology. 7th ed. 2018. p. 941–959.
3. Bacon BR, Fleming RE. Hemochromatosis. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 11th ed. 2020. p. 1172–1179.
4. Fitzsimons EJ, Cullis JO, Thomas DW, Tsochatzis E, Griffiths WJH; BSH. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). Br J Haematol 2018;181(3):293–303.
5. EASL clinical practice guidelines on haemochromatosis. J Hepatol 2022;77(2):479–502.
6. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG clinical guideline: hereditary hemochromatosis. Am J Gastroenterol 2019;114(8):1202–1218.
7. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; AASLD. Diagnosis and management of hemochromatosis: 2011 practice guideline by the AASLD. Hepatology 2011;54(1):328–43.
8. Adams PC, Jeffrey G, Ryan J. Haemochromatosis. Lancet 2023;401(10390):1811–1821.
9. Olynyk JK, Ramm GA. Hemochromatosis. N Engl J Med 2022;387(23):2159–2170.
10. Czaja AJ. Review article: iron disturbances in chronic liver diseases other than haemochromatosis — pathogenic, prognostic, and therapeutic implications. Aliment Pharmacol Ther 2019;49(6):681–701.