Metabolic and Genetic Diseases

Oren Fix, MD, MSc, FAASLD
Medical Director, Liver Transplant Program
Swedish Medical Center, Seattle, WA

Clinical Associate Professor
Washington State University
Elson S. Floyd College of Medicine

- No relevant financial disclosures
Metabolic and Genetic Diseases

Hereditary Hemorrhagic Telangiectasia

- Rendu-Osler-Weber syndrome; rare, 1-2 cases/10,000, AD inheritance
- Widespread cutaneous, mucosal and visceral AVMs (skin, mucous membranes, lung, brain, GI tract, liver)
- Mutation in TGF-beta signaling pathway genes: endoglin (ENG, type 1), activin receptor-like kinase type 1 (ALK-1 or ACVRL-1, type 2)
- Diagnosis (3 of 4): epistaxis, cutaneous or mucosal telangiectases, visceral involvement (lung, CNS, GI tract, or liver), family history of HHT
- Liver involvement results in shunting: arteriovenous, portovenous, arteriportal
- Most common initial presentation: high-output heart failure, followed by portal hypertension and biliary ischemia
- Most common biochemical abnormalities: elevated alk phos and GGT
- Liver synthetic function normal, platelet count normal, do not develop cirrhosis
Hereditary Hemorrhagic Telangiectasia

- Portal hypertension from arterioportal shunting or NRH
- “Hepatic disintegration”: bile duct and liver necrosis from biliary ischemia
- NRH and FNH (100x general population) frequently associated with liver involvement by HHT
- “Pseudocirrhosis”: liver may appear nodular (NRH)
- FNH can be mistaken for HCC
- RUQ thrill/bruit may suggest liver involvement
- Gold standard is angiography but Doppler US or multiphase CT also useful
- Avoid liver biopsy (bleeding)
- Treat biliary ischemia with UCDA, antibiotics, avoid ERCP
- LT only curative treatment for portal hypertension, high-output heart failure, acute biliary necrosis
- Non-standard MELD exception for heart failure or severe diffuse bilobar hepatic necrosis

Wilson Disease

- Inherited disorder of excessive copper accumulation
- ATP7B gene (>300 mutations identified): transmembrane transport of copper within hepatocytes
- Absent/reduced function causes decreased hepatocellular excretion into bile→hepatic copper accumulation and injury→copper release into bloodstream→organ deposition (brain, kidneys, cornea)
- Failure to incorporate copper into ceruloplasmin
- Disease spectrum: asymptomatic with only biochemical manifestations, brief clinical illness like acute viral hepatitis or autoimmune hepatitis, ALF, predominantly neurologic presentation
- Classic presentation: cirrhosis, neurological manifestations, KF rings (half of patients presenting with liver disease do not possess 2 of these 3 criteria)
- Usually <40 years old but age alone should not exclude the diagnosis
Wilson Disease

- Kaiser-Fleischer Rings
  - Copper deposits in cornea
  - Not specific for WD; found in other chronic cholestatic diseases and neonatal cholestasis
  - 44-62% of pts w/mainly hepatic disease
  - Absence does not exclude WD
  - KF rings and sunflower cataracts (copper deposits in lens) found by slit-lamp examination
  - Disappear with effective medical treatment or after LT

- Ceruloplasmin
  - Major copper carrier in blood
  - Usually decreased in WD
  - Can be low in renal or enteric protein loss or severe ESLD
  - <20 mg/dL consistent with WD, diagnostic if associated with KF rings
  - Modestly low levels need further eval
  - Normal levels do not exclude WD (acute phase reactant)

- Serum/urine copper
  - Serum copper usually decreased
  - Exception is ALF: marked increase
  - 24-hr urine copper typically >100 ug; >40 ug requires further evaluation

Wilson Disease – Liver Biopsy

- Hepatic copper content >250 ug/g dry weight is highly suggestive of WD
- <50 ug/g dry weight excludes WD (in untreated patients)
- 70-250 ug/g dry weight requires further eval
- Mild steatosis, glycogenated hepatocyte nuclei, focal hepatocellular necrosis, fibrosis
- Cirrhosis by second decade of life
- May mimic autoimmune hepatitis or NAFLD/NASH
- Hepatocyte apoptosis in WD-ALF
- Absence of copper on liver biopsy does not exclude WD
### Wilson Disease – Acute Liver Failure

- Coombs-negative hemolytic anemia, acute intravascular hemolysis
- Coagulopathy unresponsive to IV vitamin K
- Rapid progression to renal failure
- Modest increase in aminotransferases (<2000 U/L)
- AST>ALT (mitochondrial damage?)
- Normal of very low alkaline phosphatase (<40 U/L)
- Alkaline phosphatase:total bilirubin ratio <2
- Ceruloplasmin usually low
- Very high serum and 24-hour urine copper
- KF rings may be absent in 50% of patients
- F:M = 2:1
- Cirrhosis typically present even if ALF is first presentation of WD
- Requires urgent LT (status 1A)

### Wilson Disease – Treatment

**D-penicillamine**
- Promotes urinary excretion of copper
- Numerous side effects: sensitivity/allergic reaction, nephrotoxicity, lupus-like syndrome, thrombocytopenia/total aplasia, dermatologic toxicity, myasthenia gravis, polymyositis, loss of taste, retinitis

**Zinc**
- Induces enterocyte metallothionein, endogenous chelator of metals
- Can remove stored copper (unlike penicillamine and trientine)
- Generally reserved for maintenance treatment or first-line treatment in asymptomatic/presymptomatic patients

**Trientine**
- Promotes copper excretion by kidneys
- Few side effects: gastric irritation

**Treatment monitored by 24-hour urinary copper**
- Penicillamine/trientine: 200-500 ug/day (<200 ug/day indicates nonadherence or overtreatment)
- Zinc: <75 ug/day
Alpha-1-Antitrypsin (AAT) Deficiency

- Liver is primary site of AAT protein synthesis
- Primary role is to inhibit neutrophil elastase, protect lung tissue
- M: wild-type allele of SERPINA1 (serine protease inhibitor A1)
- Z, S: point mutations/severe deficiency alleles
  - Do not affect synthesis
  - Cause degradation or formation of ordered polymers (some secreted)
  - Polymers persist in ER, positive on periodic acid-Schiff staining and resistant to diastase (PAS-D), toxic – cause liver disease

AAT Deficiency – Clinical Presentation

- Liver and/or lung disease
- Chronic hepatitis, cirrhosis, HCC, rarely ALF
- Liver and lung disease risks are independent and different ages of peak incidence – same patient can have both
- Neonatal hepatitis syndrome
  - Typical presentation in neonatal period (10% of infants with PI ZZ)
  - Cholestatic jaundice, pruritis, poor feeding, poor weight gain, hepatosplenomegaly
  - Indistinguishable from extrahepatic biliary atresia, CF
- Rarely present with vitamin K-deficient coagulopathic hemorrhage
- Emphysema not observed in children – takes decades
AAT Deficiency – Deficiency Alleles

- **PI ZZ**
  - Risk of cirrhosis associated with advancing age
  - Smoking contributes to earlier/more severe lung disease

- **PI MZ**
  - Usually asymptomatic
  - Modifies risk of other liver diseases
  - Over-represented in CLD (NAFLD, alcohol, cryptogenic cirrhosis)

- **PI SZ**
  - Children rarely have clinically relevant liver disease
  - May develop liver disease identical to PI ZZ

- **Null homozygotes**
  - No circulating AAT
  - More severe lung disease
  - No increased risk of liver disease

AAT Deficiency – Diagnosis & Treatment

- **Diagnosis**
  - Measure serum AAT level, then phenotype/genotype
  - Recall that AAT is an acute phase reactant
  - Assess for advanced liver disease
  - HCC surveillance in patients with cirrhosis

- **Treatment**
  - Refer to pulmonologist
  - Augmentation therapy may reduce pulmonary disease but has no effect on liver disease
  - Avoid NSAIDs: increase AAT synthesis and hepatic accumulation
  - Smoking cessation
  - Liver transplantation
Iron Overload Syndromes

- **Hereditary hemochromatosis**
  - Inherited iron overload disorder caused by excessive iron absorption due to hepcidin deficiency
  - Hepcidin: expressed predominantly in hepatocytes, binds to ferroportin (macrophages and enterocytes), induced by excess iron or inflammation, decreased by iron deficiency, ineffective erythropoiesis, hypoxia
  - Northern European ancestry (Nordic/Celtic): prevalence 1/250
  - Cirrhosis, HCC, diabetes, cardiomyopathy, hypogonadism, arthropathy, skin pigmentation
  - C282Y homozygotes account for 80-90% of typical HH
  - Low penetrance: 70% of C282Y homozygotes have phenotypic expression, 10% develop severe iron overload and organ damage

- **Secondary iron overload**

---

Iron Overload Syndromes

- **Type 1 HH (HFE)**
  - HFE mutations (C282Y, H63D, S65C)
  - Grade 4 stainable iron in hepatocytes with periportal distribution
  - Lack of stainable iron in Kupffer cells

- **Type 2 HH (juvenile hemochromatosis)**
  - Mutations in hemjuvelin (HJV) or hepcidin (HAMP)
  - Early onset (<30 years old)
  - Cardiomyopathy, hypogonadism prevalent
  - Same biopsy findings as type 1

- **Type 3 HH**:
  - TfR2 mutations
  - Same biopsy findings of type 1

- **Type 4 HH (ferroportin disease)**
  - Only AD form of HH
  - Mutations in FPN1 gene (SLC40A1)
  - Spleen is most affected organ (high FPN1 activity in macrophages)
  - Iron preferentially in Kupffer cells
  - MRI can distinguish from HFE-HH
### Iron Overload Syndromes – Clinical Features

- Fatigue and arthralgias (2nd and 3rd MCP joints) are most common early symptoms
- Additional symptoms: RUQ pain, chondrocalcinosis, impotence, decreased libido, heart failure, diabetes
- Signs: hepatomegaly, testicular atrophy, skin pigmentation, changes of PCT
- Women present ~10 years later (menstrual blood loss, maternal iron loss during pregnancy)
- Alcohol is main modifier associated with HH-related cirrhosis

### Iron Overload Syndromes – Diagnosis

- Elevated ferritin levels + C282Y homozygosity or C282Y/H63D compound heterozygosity
- Normal ferritin (<200 ug/L in premenopausal women, <300 ug/L in men/postmenopausal women) + transferrin saturation <45% has 97% NPV for excluding iron overload
- Ferritin can be elevated in absence of increased iron stores: alcoholic liver disease, chronic HBV/HCV, NAFLD, lymphomas, chronic inflammatory conditions
- Ferritin <1000 ug/L predicts absence of fibrosis, no need for liver biopsy unless concomitant excessive alcohol use or elevated liver biochemistries
- Liver biopsy: HIC >71 mmol/g dry weight, HII >1.9 (HII = HIC/age)
**Iron Overload Syndromes – Treatment**

- Phlebotomy weekly as tolerated until target ferritin 50-100 ug/L
- Improved with phlebotomy: fatigue, skin pigmentation, insulin requirements for diabetics, abdominal pain, cardiomyopathy, liver fibrosis (13%-50%)
- Irreversible despite phlebotomy: arthropathy, hypogonadism, advanced cirrhosis, insulin-dependent diabetes
- Normal life expectancy when patients are treated before onset of cirrhosis or diabetes
- Continue HCC surveillance in patients with cirrhosis following phlebotomy
- Liver transplantation

**Iron Overload Syndromes – Secondary**

- **Causes**
  - Ineffective erythropoiesis (e.g., thalassemia, sickle cell anemia), parenteral iron overload, liver disease, malignancy, chronic inflammatory states
  - Consider liver biopsy in patients with iron overload who are not C282Y homozygotes or compound heterozygotes
    - Pattern of iron distribution similar to type 4 HH (primarily in Kupffer cells rather than periportal hepatocytes)
  - MRI can also show splenic iron deposition (absent in HFE-HH)
- Phlebotomy useful in some forms of secondary iron overload and in patients with PCT
- No evidence that phlebotomy is beneficial in alcoholic liver disease
- Iron chelation is treatment of choice for iron overload from ineffective erythropoiesis
  - Deferoxamine (IV/SC), deferiprone (oral), deferasirox (Exjade, oral)
Mitochondrial Defect

- Clinically heterogeneous (single organ or multisystem)
- Heterogeneous presentation: neonatal acute liver failure, lactic acidosis, cholestasis, chronic liver failure
- Suspect mitochondrial disorder when:
  - Neuromuscular symptoms + liver dysfunction
  - Multisystem involvement in patient with acute or chronic liver disease
  - Rapidly progressive course of liver disease
  - Presence of lactic acidosis (not present in all disorders), hepatic steatosis, or ketonemia
- Abnormal liver biopsy: micro/macroversicular steatosis, cholestasis, hepatocellular degeneration/swelling, lobular inflammation, portal fibrosis, cirrhosis
- LT survival <50%; unrecognized neurologic involvement pre-LT may progress rapidly post-LT
- Significant neuromuscular or cardiovascular involvement are absolute contraindications to LT

Cystic Fibrosis

- Most common AR systemic disease of newborns in US
- Mutations in CF transmembrane conductance regulator (CFTR) protein
- CFTR located on apical surface of cholangiocytes, not on hepatocytes
- CFTR mutations cause: viscous bile, decreased bile flow and alkalinity, biliary mucus plugging, periductal inflammation, cholangiocyte damage, bile duct proliferation, periductal fibrosis, hepatic steatosis
- CF liver disease (CFLD) is umbrella term for:
  - elevated liver enzymes
  - hepatic steatosis
  - neonatal cholestasis
  - focal biliary cirrhosis
  - multilobular cirrhosis
  - cholangiopathy
- Clinically important CFLD includes biliary cirrhosis and portal hypertension
**Cystic Fibrosis**

- 25% of CF patients with portal hypertension have cirrhosis, rest have non-cirrhotic portal hypertension (pre-sinusoidal from obliterative venopathy)
- Endoscopy complicated by increased risk of anesthesia
- Variceal band ligation preferred to NSBB because of bronchoconstriction
- UDCA most commonly used drug for CFLD despite controversy/limited data
- LT alone contraindicated in:
  - active pulmonary infection
  - FEV1 <50%
  - extensive pulmonary fibrosis
  - pulmonary hypertension (>35 mmHg)
- Standardized MELD/PELD exception for LT:
  - Diagnosis confirmed by genetic analysis and FEV1 <40% predicted
  - ≥18 years: MMaT-3
  - 12-17 years: MMaT
  - <18 years: MPaT

**Fibrocystic Diseases – Choledochal Cysts**

- Choledochal cysts are rare congenital cystic dilations of biliary tract
- Complications: malignant transformation, cholangitis, pancreatitis, cholelithiasis
- Incidence: 1/100,000-1/150,000 in Western countries, 1/13,000 in Japan
- 80% diagnosed in infants/young children, F:M = 4:1
- Anomalous pancreaticobiliary duct union (APBDU) in 30%-70%
- Congenital cardiac abnormalities in 31% of pediatric patients
- 10-30% incidence of cancer
  - Rare in children
  - Dismal prognosis
  - Most common in types I and IV, rare in II, III, V
- MRCP is diagnostic modality of choice for infants/children
  - Direct communication between biliary tree and cystic duct
Fibrocystic Diseases – Choledochal Cysts

Type I
- 60%-80% of CCs
- Can include mild intrahepatic dilatation from biliary stasis
- Managed with complete extrahepatic bile duct excision + R-en-Y HJ

Type II
- 2% of CCs
- Diverticula of CBD
- Malignant transformation rare
- Managed by simple excision or diverticulectomy

Type III
- 1%-4% of CCs
- “Choledochocoele”
- Intraduodenal at pancreaticobiliary jcn
- Managed primarily endoscopically (e.g., sphincterotomy)
- Malignant transformation rare

Type IV
- 15%-20% of CCs
- Managed with complete extrahepatic bile duct excision (IVB) or hepatectomy (IVA)

Type V
- Caroli’s Disease
- Low risk of malignant transformation (7%)
- Managed by liver resection or LT

Due to ductal plate malformation, associated with polycystic kidney disease
- 1/1,000,000, F:M = 1:1, >80% before age 30, can be asymptomatic up to 20
- Main presentation: recurrent acute cholangitis
- Classic triad (rare, usually children): abdominal pain, jaundice, RUQ mass
- Also: liver abscesses, intra/extrahepatic stones, acute/chronic pancreatitis, cholangiocarcinoma, portal hypertension, cirrhosis
- Differential: PSC, recurrent pyogenic cholangitis, polycystic liver disease
- Caroli Syndrome = type V CCs + congenital hepatic fibrosis
- “Central dot sign”: portal vein enhancement surrounded by dilated intrahepatic bile ducts on MRCP or contrast CT
- Surgical management or LT indicated because of cholangitis or liver disease rather than malignant potential
**Familial Amyloid Polyneuropathy (FAP)**

- Multisystem condition due to mutations in transthyretin (TTR) gene (formerly prealbumin), now called hereditary transthyretin amyloidosis (hATTR)
- Over 120 TTR variants, Val30Met most common
- Involves sensory-motor and autonomic nervous system, heart, kidney, ocular vitreous, death within 10 years of clinical presentation
- Diagnosis: tissue biopsy w/Congo red staining, IHC or MS to confirm TTR
- Treatment includes LT (>90% of circulating TTR produced in the liver)
- Liver is otherwise structurally/functionally normal
- FAP is most common source of domino livers
- Iatrogenic FAP in domino liver recipient, often at accelerated pace (7-9 yrs)
- Standardized MELD exception (all of the following):
  - Waitlisted for heart transplant or echo with EF >40%, can walk without assistance, confirmed TTR gene mutation, biopsy-proven amyloid

---

**Erythryopoietic Protoporphyria (EPP)**

- Cutaneous porphyria, overproduction of protoporphyrin by bone marrow
- Complex inheritance, M:F = 1:1, 2 types:
  - Ferrochelatase deficiency ("classical" EPP)
  - Delta aminolevulinic acid synthase 2 hyperactivity (X-linked protoporphyria)
- Symptoms start in early infancy: painful photosensitivity without blisters
  - Stinging, burning, itching on sun-exposed skin, mild swelling/erythema, hyperkeratosis/lichenification with repeated injury, urine color is normal
- Biliary system exposed to high concentrations of protoporphyrin, highly toxic
  - Cholelithiasis (pigment gallstones) before age 30 (20% of patients)
  - Biliary obstruction, inflammation, fibrosis, cirrhosis, liver failure
- Diagnosis: fluorescent erythrocytes (flurocytes), measure total blood porphyrin (high free protoporphyrin), increased fecal protoporphyrin
- Treatment: Avoid sunlight, oral beta-carotene, activated charcoal/cholestyramine, afamelanotide (alpha-melanocyte-stimulating hormone analogue), LT + BMT
### References

#### Hereditary Hemorrhagic Telangiectasia
  - https://www.journal-of-hepatology.eu/action/showPDF?pii=S0168-8278%2806%2900687-9
  - https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S0168827815008474.pdf?locale=en_US&searchIndex=

#### Wilson Disease

#### Alpha-1-Antitrypsin Deficiency
  - https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1088026618300016.pdf
  - https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1542356511013899.pdf

#### Iron Overload Syndromes
- Kowdley KV et al. ACG clinical guideline: hereditary hemochromatosis. Am J Gastroenterol 2019;1202
  - https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1088026619300016.pdf
  - https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1088026619300016.pdf
- Teckman JT et al. Erythropoietic protoporphyria. Orphanet J Rare Dis 2009;4:19
  - https://doi.org/10.1186/1750-1172-4-19

#### Mitochondrial Defect

#### Cystic Fibrosis
  - https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1088026619300016.pdf

#### Fibrocystic diseases
  - https://www.journals.org/action/showPdf?pii=S1072-7515%2814%2900054-3

#### Familial Amyloid Polyneuropathy
  - https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S0055470511000023.pdf?locale=en_US&searchIndex=

#### Erythropoietic Protoporphyrinopathy (EPP)
- Leca M et al. Erythropoietic protoporphyria. Orphanet J Rare Dis 2008;4:19