

Prevalence: Hemochromatosis 1:200 vs A1AT 1:1600 vs Wilsons 1:50000

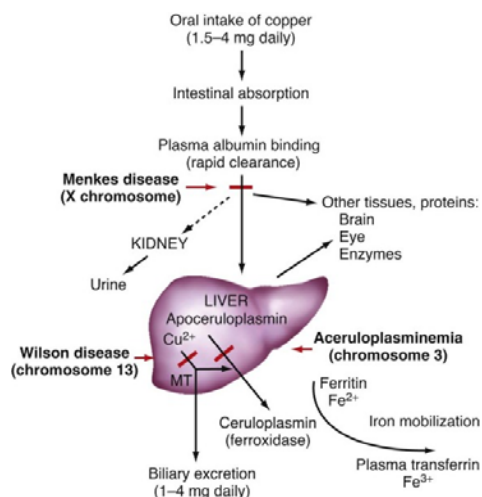
Primarily Pediatric (refer to peds section)

- Types
 - **Glycogen Storage Disease** (pathways responsible for creating and breaking down glycogen to glucose, Type I/III/IV are most common, additional Sx include neutropenia w/ recurrent infections, 22-75% of pts develop hepatic adenomas during 2nd decade of life and rarely transform to HCC)
 - **Congenital Disorders of Glycosylation** (pathways responsible for creating the glycan moieties used for intracellular trafficking of multiple proteins including albumin, hormones, lipoproteins, etc, Ia/Ib/Ic are most common)
 - **Tyrosinemia** (pathways responsible for the catabolism of phenylalanine/tyrosine, also there is damage to kidneys, an interesting Tx using the herbicide NTBC has become the mainstay of Tx)
 - **Urea Cycle Defects** (pathways responsible for the removal of NH₄ for AA catabolism by converting it into urea, Tx includes protein restriction and hemodialysis)
 - **Mitochondrial Liver Disease** (respiratory chain oxidative phosphorylation electron transport system, 2/2 mutated mitochondrial DNA derived from maternal ova)
 - **Bile Acid Synthesis/Transport Defects** (refer)
 - **Cystic Fibrosis** (refer)
- S/S
 - manifest as acute life-threatening illnesses similar to an infection during the neonatal period BUT rarely they can present as chronic liver disease in adults
 - consider in a neonate w/ neuromuscular dysfunction, dysmorphisms, hyperammonemia, hypoglycemia, lactic acidosis, unusual odors, HSM, failure to thrive, developmental delays, dietary aversions, FHx of consanguinity, multiple miscarriages, early infant deaths, relatives w/ unexplained liver dz
- Dx
 - labs could be abnormal ONLY during acute attacks
 - always Bx liver and keep frozen sections to look under EM
- Tx
 - usually can be Tx w/ dietary restrictions but sometimes liver transplant is needed

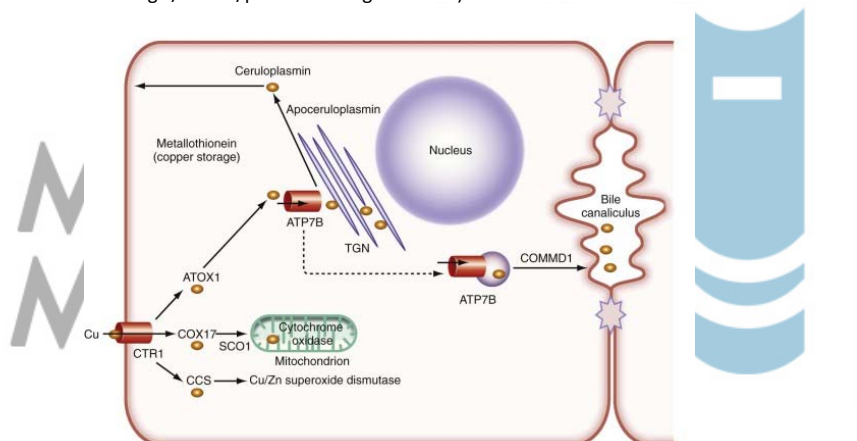
Primarily Adult

Wilson's Disease aka Hepatolenticular Degeneration

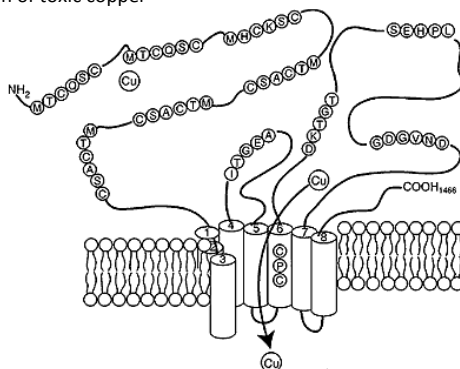
- Copper Metabolism & Mechanism
 - Typical Western diet ~2mg/d (RDA: 0.9mg/d, green vegetables and fish) of copper w/ 50% bioavailability at the proximal SI thus ~1mg/d is excreted into feces
 - Menke's Disease (X-linked defect in intestinal absorption of copper)
 - Occipital Horn Syndrome aka X-Linked Cutis Laxa (mild form of Menke's Disease)
 - Copper is released into the portal circulation bound to albumin and then avidly picked up by other cells that require copper via hCTR1 transporter
 - 1° Hepatocytes
 - 2° Neurons, Epithelial Cells, etc
 - Within cells various chaperones (glutathione, metallothionein, HAH1, etc) direct copper to specific target enzymes where it acts as a cofactor
 - Lysyl Oxidase (cross links elastin)
 - Superoxide Dismutase (free radical scavenging)
 - Cytochrome Oxidase (electron transport system)
 - Tyrosinase (pigment production)
 - Dopamine Monooxygenase (dopamine production)



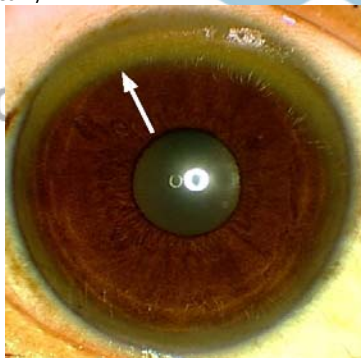
- Copper homeostasis is maintained within hepatocytes via the ATP7B protein which (1) traffics excess copper to bile canaliculus for excretion (<1mg/d) and (2) binds copper to apoceruloplasmin forming holoceruloplasmin (fxn: multifunctional oxidase that in addition controls iron efflux out of cells, hence it plays NO essential role in the metabolism of copper, it just uses copper as a cofactor)
- **Aceruloplasminemia (AR mutation resulting in absence of ceruloplasmin → hemosiderosis → neurologic/retinal/pancreatic degeneration)**



- **ATP7B Gene**
 - Locus: 13p1
 - Protein: 1443 Residues, 160kd
 - Activity: Hepatocytes
 - Mutation: AR
 - What Happens? uncomplexed copper accumulates in hepatocytes inducing oxidative damage → hepatocytes die releasing uncomplexed copper → copper deposits in other organs causing other organ damage → cells attempt to deal with rising levels of intracellular copper by binding copper to metallothioneins creating non-toxic aggregates → as the disease progresses copper exceeds storage capacity of metallothioneins resulting in accumulation of toxic copper



- Epidemiology
 - Occurs world wide w/ no clear ethnic predilection
 - 1/30k in most populations w/ 1% carries
 - Case reported in 2yo and 70yo however a majority of cases present b/t 5-40yo (not just a pediatric disease anymore)
 - Presentation is variable w/ 50% are young pts (~15yo) p/w liver dz and 50% are older pts (~18yo) p/w CNS dz
- S/S
 - Liver
 - Types
 - Acute: Asymptomatic Abnormal LFTs to Acute Hepatitis to Acute Liver Failure (**characteristic hemolysis and renal failure**)
 - Chronic: Asymptomatic Abnormal LFTs to Chronic Hepatitis to Cirrhosis
 - NB interestingly pts can look very much like (1) AIH w/ elevated IgG and auto-antibodies including ASMA thus consider WD in pts who are unresponsive to AIH Tx and (2) NAFLD w/ steatosis on Bx
 - NB importantly it is one of the few chronic liver disorders that can present w/ ALF uniquely characterized by concurrent hemolytic anemia and rapidly progressive AKI, WD represents 19/1213 (~1.6%) of cases in the US-ALF-Study from 1998 to 2007
 - NB no increased r/o HCC except if cirrhotic (no pre-cirrhotic screening is recommended)
 - MRI (multiple hypodense nodules w/ hyperdense septa and perihepatic fat layer)
 - CNS
 - Types (Parkinsonian-like changes)
 - Movement Disorder: tremors, ataxia, poor coordination, loss of fine motor skills
 - Dystonia: rigidity, spasticity, mask-like facies, pseudobulbar Sx w/ dysarthria/dysphagia/hypophonia
 - Peripheral Neuropathy: dysautonomia
 - Psychiatric Changes: depression, behavioral changes (impulsive, aggressive, antisocial), personality changes, psychosis
 - NB seizures and cognitive impairment is rare
 - NB MRI shows T2 hyperintensity in basal ganglia specifically the lenticular nucleus
 - Eye
 - Kayser-Fleischer (KF) Rings
 - Described by Kayser and Fleisher in 1902
 - Copper deposits w/in Descemet's Membrane of the Limbus of the Cornea
 - brown-gold-yellow-green ring beginning where the cornea and sclera meet moving in centrally
 - no change in vision
 - sometimes can be seen in normal light but generally a slit-lamp is needed
 - can be seen in chronic cholestatic conditions
 - present in ~50% of pts w/ liver dz and ~100% of pts w/ CNS dz
 - resolves w/ Tx



- Sunflower Cataracts
 - Described by Siemerling and Oloff in 1922
 - Copper deposits w/in the lens
 - centrifugal cataracts
 - no change in vision
 - generally a slit-lamp is needed
 - resolves w/ Tx



- CBC
 - Coomb's Negative Hemolytic Anemia (2/2 sudden release of copper into serum specifically during ALF)
- Kidney
 - Fanconi's Syndrome (Type II Proximal RTA, Aminoaciduria, Phosphaturia, Glycosuria, Uricosuria)
 - AKI w/ Hypouricemia (occurs during ALF)
- Bone
 - Osteoarthritis, Osteoporosis, Osteomalacia
 - Blue "Azure" Lunula

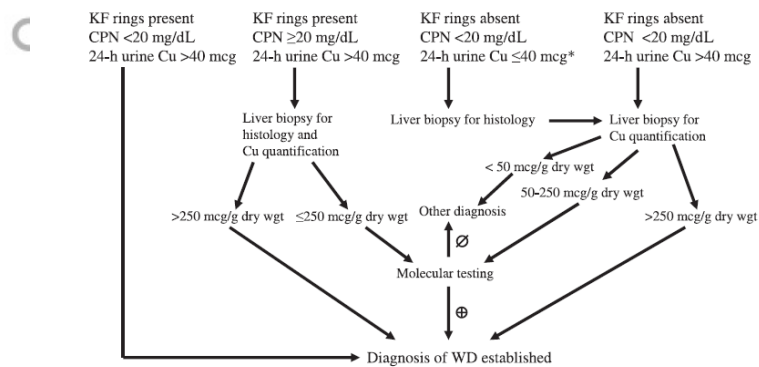


- CV
 - Cardiomyopathy
- Endocrine
 - Hypoparathyroidism
 - Amenorrhea/Infertility
- GI
 - Pancreatitis

• Diagnosis

Unexplained liver disease

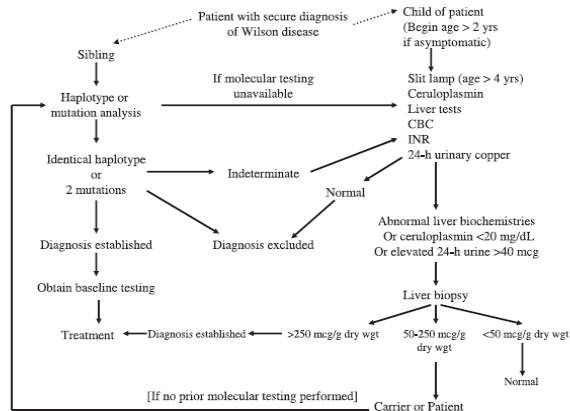
Serum ceruloplasmin (CPN); 24-h urinary Cu; slit lamp examination



- Approach
 - Screening: spot serum Ceruloplasmin is usually the first screening test and if + then 24-Hour Urine Copper and Slit-Lamp Exam
 - KF Rings + Spot Serum Ceruloplasmin + 24hr Urine Copper BUT if you don't meet all three criteria (just two) then get a liver Bx ± genetic testing
 - NB heterozygotes can have borderline levels
- Suggestive LFTs
 - Variable LFTs
 - During ALF
 - AST/ALT >2.2 and mild <10xULN

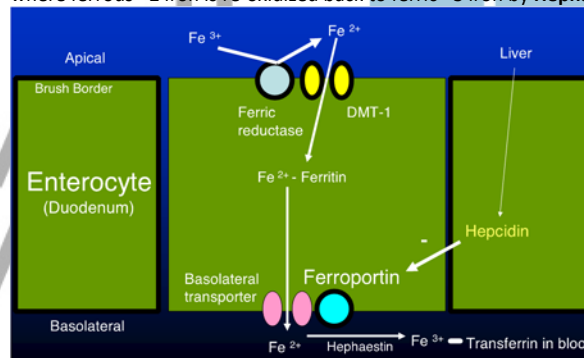
- AST>ALT b/c of the unique damage to mitochondria which holds additional AST
 - AP/TB <4
 - Low AP b/c copper displaces zinc as the co-factor for AP
 - High TB from additional hemolysis
 - Copper Studies
 - Serum Ceruloplasmin <20mg/dL (nl: 20-60mg/dL)
 - Decreased: malnutrition, protein losing enteropathy, end stage chronic liver dz, nephrotic syndrome, et al
 - Increased: any inflammatory state as it is an APR (hence can be falsely normal in acute hepatitis, etc) and high estrogen states (hence can be falsely normal in pregnancy, OCP use, etc)
 - Not very specific b/c made in liver such that 50% of ALF pts have low ceruloplasmin
 - 24hr-Urine Copper >40µg/d (nl: <20-40µg/d)
 - Total Serum Copper (unreliable test)
 - even though copper overload disorder serum copper is decreased in mild chronic WD vs normal in severe chronic WD vs high only in ALF
 - suggestive if >80mcg/mL
 - Liver Bx (never ask for "copper stain" b/c non-specific rather send off to Mayo for "copper quantification")
 - Hepatic Copper >250µg/g of dry weight liver (nl: <50µg/g)
 - often as high as 3000µg/g
 - chronic cholestasis (PBC, PSC, etc) and AIH can have mildly elevated copper (150-350)
 - Light Microscopy
 - Early: micro/macrovessicular steatosis, balloon degeneration and councilman bodies, periportal inflammation (NB most copper in early disease is bound to metallothionein and thus is not detected by copper stains)
 - Late: fibrosis to cirrhosis (NB most copper in late disease is free and thus can be detected by copper stains (Rhodamine and Victoria Blue)) Ex: Liver section w/ Rhodamine stain demonstrating a nodule w/ heavy copper deposition w/ adjoining liver tissue w/ minimal staining
-
- Electron Microscopy
 - Occasionally light microscopy is not helpful and in this instance electron microscopy shows very specific mitochondrial changes
 - Genetic Testing w/ ATP7B gene point mutation
 - there is not one common mutation rather there are about 300
 - point mutations resulting in AA substitutions and missense/nonsense/deletion mutations
 - H1069Q is seen in 20% of pts of European descent
 - otherwise alleles are equally common therefore most pts are compound heterozygotes hence rarely assessed b/c expensive
 - if the diagnosis is questionable then whole gene sequencing can be done
 - haplotype analysis or specific analysis of a known mutation can be used for family screening of a first degree relative
 - mutations are catalogued at <http://www.wilsonsdisease.med.ualberta.ca/database.asp>
 - Treatment
 - (1) Acute Liver Failure
 - it is the one cause of ALF where pt may already have cirrhosis
 - decrease copper w/ CVVHD and plasma exchange
 - some try chelators and uptake inhibitors but generally not effective acutely
 - all pts uniformly need a transplant
 - 1/5/10yr survival is 85,76,60%
 - contraindicated if severe neurologic impairment

- Nazer Score (includes TB, AST, PT) helps to further stratify ALF pts w/ a score of >7 indicating near universal mortality w/o transplant
- transplant corrects the underlying metabolic problem thus no medical Tx is needed thereafter
- (2) Chronic: Symptomatic Dz or Abnormal Labs
 - prognosis all depends on degree of organ damage
 - NB neurologic Sx inconsistently resolve after medical treatment or transplant
 - Induction w/ chelators to quickly bring copper down to non-toxic levels
 - Mech: mobilize copper out of cells followed by cupruresis
 - D-Penicillamine (Cuprimine) start w/ 250mg PO Qd then increase Qwk by 250mg/d to a maximum dose of 1000-1500mg/d divided TID (>2hr from meals b/c food inhibits absorption) NB concurrently give Pyridoxine (VitB6) 25mg PO QD to avoid deficiency
 - Goal: 24hr-Urine Copper of <500mcg/d
 - no more b/c they will be copper deficient and no less b/c not strong enough
 - some look at serum non-ceruloplasmin bound copper which should be nl
 - clinical improvement occurs w/in 2mo
 - SEs (20% of pts have significant SEs which necessitates switching to trientine)
 - Early: fever, non-specific rash, LAD, pancytopenia, initial temporary worsening of neuropsych Sx in 10% of pts therefore consider trientine in pts w/ significant neuropsych Sx
 - Late: nephrotic syndrome, SLE-like, MG-like, Goodpasture's syndrome, trace metal deficiency b/c chelates other metals, unique rash (Elastosis Perforans Serpiginosa and Progeria esp at neck b/c penicillamine interferes w/ collagen formation, in addition there is impaired wound healing)
 - Trientine (Syprine) 750-1500mg/d PO QD divided TID
 - Not as potent as penicillamine but less SEs and does not temporarily worsen neuropsych Sx
 - SEs: hemorrhagic gastritis, SLE-like syndrome, sideroblastic anemia
 - If pts are refractory to induction therapy then liver transplantation is the next step
- (3) Chronic: Asymptomatic Dz and Normal Labs AND once Chelator therapy has achieved 24hr urine copper <500
 - Lifelong Maintenance w/ Uptake Inhibitor (to keep copper below toxic levels)
 - Mech: preventing SI absorption promoting stool excretion (complex mechanism in which zinc induces metallothionein production in the enterocyte which binds copper preventing full absorption and enterocytes shed in normal turnover copper is lost into stool)
 - Zinc Salt (any type is effective but acetate is best tolerated) (Galzin) 50mg PO TID (>2hrs from meals b/c not as effective)
 - Goal: 24hr-Urine Copper of <75mcg/d (different than chelators b/c copper is never absorbed in the first place)
 - SEs: gastritis, subclinical pancreatitis, mild immunosuppressant effect
 - Tetrathiomolybdate 20mg PO TID w/ each meal and 60mg PO Qhs (investigational use)
 - SEs: pancytopenia, hepatotoxicity, neurologic changes, anti-angiogenic effect
 - Other
 - Dietary Restriction of Copper Rich Foods (never sole therapy): organ meats, chocolate, nuts, shellfish, mushrooms, beans, peas, dried fruit
 - NB check copper levels in water esp if well water or water supplied by copper pipes
 - NB avoid copper containing kitchen utensils
 - Anti-Oxidants: Vitamin E (b/c excess copper causes oxidative damage various anti-oxidants are being looked at but no controlled studies have been performed)
 - NB some continue chelators at a lower dose for maintenance therapy but remember to never give chelators and uptake inhibitors at the same time b/c uptake inhibitors bind chelators in GI tract
- Family Screening: all first degree relatives, haplotype analysis (not direct mutation analysis) if sibling vs standard serum/urine markers & PEX if child

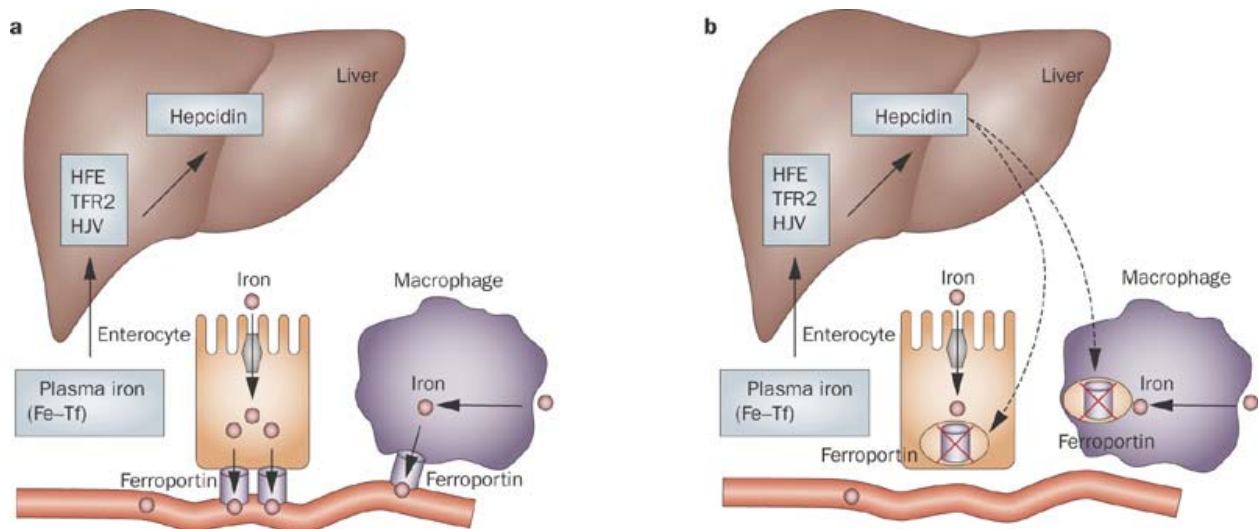


Hereditary Hemochromatosis (HHC)

- Mechanism (constitutive iron absorption)
 - Normal Iron Metabolism
 - normal Western diet has 10-20mg/d of iron but only 10% (1-2mg/d which is RDA) is absorbed by DUODENAL enterocytes via apical **Divalent Metal Transporter (DMT-1)** after it is reduced from ferric +3 to ferrous +2 state via **Ferric Reductase** located on the luminal surface of enterocytes
 - NB vitamin C increases absorption
 - iron is briefly bound to **Ferritin** in the enterocyte and then released into serum via basolateral **Ferroportin** where ferrous +2 iron is re-oxidized back to ferric +3 iron by **Hephaestin** and then bound to **Transferrin**

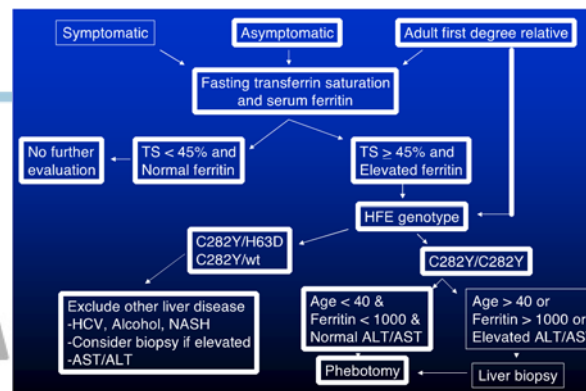


- **Iron-Transferrin** floats around the body and is incorporated or stored in various ways
 - ½ incorporated into hemoglobin in RBCs
 - ½ incorporated into myoglobin in skeletal muscle
 - ¼ stored in the reticuloendothelial system: spleen, BM, liver
 - 1/1000 incorporated into cytochromes/enzymes of the ETS in mitochondria
- when **[Iron-Transferrin]** increases it binds to the **HFE - Hemojuvelin (HJV) - Transferrin Receptor-2 (TFR-2)** in liver which in turn stimulates release of hormone **Hepcidin** from liver which in turn **inhibits Ferroportin** from releasing iron from enterocyte and as these enterocytes senesce they slough off removing 1-2mg of iron from the body keeping serum levels constant
 - In Type I HH there is a mutation of the HFE gene and thus it is unable to sense rising [Iron-Transferrin] and thus unable to stimulate Hepcidin release to prevent Ferroportin from releasing iron
 - NB Hepcidin increases not only w/ high iron but also w/ inflammation via IL-6 vs decreases w/ hypoxia

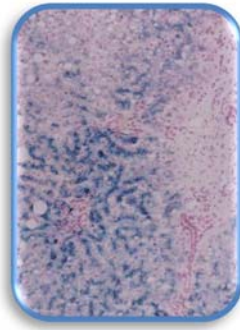


- Types of Iron Overload States (NB Hemosiderosis is a general term used to describe any type of iron overload state including hemachromatosis but also secondary causes)
 - Pathogenesis: deposition of iron in hepatocytes which induce free oxygen radicals which lead to cell injury via lipid peroxidation and subsequent scarring as the initial manifestation → as hepatocytes die they release iron which in turn deposit in other organs causing other organ damage later on
 - HH or Primary Iron Overload 2/2 Constitutive Iron Absorption
 - HFE Related HH (Type 1)
 - Incomplete Penetrant AR Mutation of the HFe gene at Chr 3
 - HFE gene point mutations (1° **C282Y 90%** 2° **H63D 10%** 3° others)
 - NB 10% carrier frequency in Caucasians of Northern European descent w/ 1/250 homozygous making it the most common inherited single gene mutation
 - Why so common? Developed 2000yrs ago as a selective advantage in Neanderthals who had a low iron diet and often had parasitic infections that resulted in iron loss
 - C282Y/C282Y (highest risk but incomplete (50-90%) penetrance as some homozygous pts have no dz esp if their iron indices are normal), C282Y/H63D (lowest risk), C282Y/WT (no risk), H63D/H63D (no risk), H63D/WT (no risk)
 - Non-HFE Related HH
 - Hemojuvelin (Type 2A)
 - Hepcidin (Type 2B)
 - Transferrin Receptor (Type 3)
 - Ferroportin (Type 4) aka African Iron Overload aka Bantu Hemosiderosis
 - it was thought to be a disorder in which excessive amounts of iron were ingested from alcoholic maize-fermented beverages brewed in iron drums but recently it is suggested that this disorder is 2/2 to AD mutation of a ferroportin
 - Secondary Iron Overload
 - Ineffective Erythropoiesis (Aplastic Anemia, Chronic Hemolytic Anemia, Thalassemia)
 - Liver Disorders (Steatosis, HCV/HBV, PCT)
 - Parenteral Iron Overload from Transfusions, Iron Infusion, Hemodialysis
 - Any Chronic Liver Disease
 - Insulin Resistance Syndrome w/ Iron Overload
 - Dietary Iron Overload
 - Other
 - Aceruloplasminemia
 - Congenital Atransferrinemia
- S/S (in order of incidence, some pts are asymptomatic but diagnosed on incidental iron studies, cause of mortality: HCC > Cirrhosis > DM and CM)
 - Constitutional (reversible)
 - Fatigue/Malaise/Lethargy (most common Sx)
 - Liver (reversible unless cirrhosis)
 - Asymptomatic Dz → Chronic Hepatitis → Cirrhosis (100%) (~40yo M>F but older in women b/c menstrual/pregnancy loss of blood aka “natural phlebotomy”)
 - HCC (pts MAY have higher risk even w/o cirrhosis)
 - Hepatomegaly is the most common presenting symptom!!!
 - Skin (reversible)

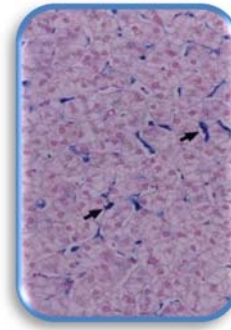
- Bronze/Slate Colored Skin (90%) not due to iron-deposition in skin BUT iron stimulating melanocytes to make more melanin
 - Pancreas (reversible)
 - Type 2 Diabetes Mellitus (65%)
 - Joints (irreversible)
 - 2nd/3rd MCP (first two knuckles), PIP, Wrists, Hips, Knees, Ankles Arthropathy (35%, subchondral sclerosis, cyst formation, irregular joint space narrowing, osteophyte formation = classic degenerative disease, NB pseudogout can also occur)
 - Endo (irreversible, iron is typically affecting the pituitary gland not the endocrine organs nevertheless the only end organs that are damaged are the gonads and the thyroid)
 - Hypogonadism
 - Hypothyroidism
 - Heart (reversible)
 - Dilated CHF
 - Arrhythmias
 - Infections (reversible, b/c they require iron)
 - *Vibrio, Listeria, Yersinia*
- Diagnosis (rule out secondary hemosiderosis, 75% discovered based on incidental labs, Screen w/ % Sat and if >45% then Confirm w/ Genetic Testing and then if needed liver Bx, Ferritin, LFTs)



- 1st Iron Studies (SCREENING)
 - %Sat >45% but usually >90% (%Sat = Iron/TIBC, TIBC aka transferrin, nl 20-45%, if <45% then no further w/u)
 - Other: High Ferritin, High Iron, Low TIBC
 - False Negative: **young age** (values increase w/ age)
 - False Positive: **recent iron use, Chronic Viral Hepatitis, ALFD, NAFLD, PCT, Inflammation, Malignancy** (can have abnormal iron indices esp ferritin hence you need genetic confirmation)
- 2nd Genetic Testing (CONFIRMATION)
- 3rd Question: Who needs a liver biopsy? Answer: based on age, Ferritin and LFTs (refer to flow chart)
 - Why? because when abnormal LFTs, Ferritin >1000ng/mL, Age >40yo then there risk of having cirrhosis is much higher which is important to know when assessing prognosis
 - Iron Load
 - Hepatic Iron Concentration (HIC) (nl 300-1500 mcg/g dry weight)
 - Asymptomatic (1.5-10k)
 - Symptomatic (10-20k)
 - Cirrhosis (>20k)
 - Hepatic Iron Index (HII) [mmol of iron / g of dry liver / pt age] NB developed b/c HIC progressively increases w/ age in pts w/ HH however this is not the case for secondary hemosiderosis but w/ the advent of genetic testing it is no longer calculated (nl <1.1)
 - Theory: [iron] increases progressively w/ age in homozygous HH while heterozygous HH and secondary causes do not hence HII would >1.9 in homozygous HH while it would be >1.9 in heterozygous HH and secondary causes BUT this is not always the case hence it is not done much anymore esp since the advent of genetic testing
 - Perls' Prussian Blue Stain
 - Early (Zone 1, w/in hepatocytes) → Late (Zone 1,2,3 gradient, w/in not only hepatocytes but also Kupffer Cells and Bile Duct Cells) → Cirrhosis (micronodular)
 - NB iron can also be seen in Viral, AFLD, NAFLD but there is no gradient from Zone 1 to 3



Primary Overload
(iron in Hepatocytes)



Secondary Overload
(iron in Kupffer Cells)

- Other: Imaging (only sensitive when significant iron overload)
 - CT
 - “white liver” = homogenous increased density
 - NB only other process that can do this is amiodarone toxicity
 - MRI
 - “black liver” = homogenous increased intensity
 - You can actually quantify iron content in the liver allowing for repeated measures
- Screen
 - Who? Abnormal Iron Studies, Clinical S/S, First Degree Relatives, Chronic Liver Dz in Caucasians, Liver Dz + DM, Liver Dz + Heart Dz, PCT, Premature Sexual Dysfunction
 - Some have argued for mass general population screening
- Treatment (if Dx and Tx early then pts can have a normal lifespan)
 - Phlebotomy: 500cc aka 1-Unit of whole blood (~250mg of iron) Qwk until Ferritin <50ng/mL (check Q2mo, takes about a few years to achieve, Ferritin falls ~30ng/mL per unit of whole blood) then maintenance (usually 3-6x/yr) to keep in range but don't phlebotomize if it will bring Hct to <37
 - Chelators: Deferoxamine 20-50mg/kg/d SC continuous infusion over 12hrs 5d/wk via a portable pump (if cardiac involvement OR unable to undergo phlebotomy)
 - Pts who undergo successful phlebotomy b/f cirrhosis have survival comparable to age-matched controls but those w/ cirrhosis have a 10yr survival of ~60% w/ HCC and hepatic failure being the most common cause of death
 - DM makes prognosis much worse!!!
 - if liver transplant is done then 1yr survival is ~60% (pts don't do as well as other liver transplant pts b/c of the other organs affected esp heart and infections)
 - Does Not Improve: cirrhosis, arthropathy, endocrinopathy
 - Genetic Counseling
 - Vaccinate, Avoid Hepatotoxins
 - Avoid Vitamin C which promotes iron absorption and iron containing foods (MVI, meats, liver, clams/oysters/mussels, etc)

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α1-Anti-Trypsin (AAT) Deficiency

- Epidemiology
 - Prevalence: 60-100k (US) have symptomatic AAT but likely 3/4 unrecognized, likely represents 1% of COPD
 - Incidence: 1/4000 (US), similar to Cystic Fibrosis
 - Ethnicity: White>Hispanic>Black>Asian
 - Important Points: one of the most common genetic diseases in the world, most common metabolic disease affecting the liver, most common metabolic disease for which transplant is performed
- Basics of Alpha 1 Anti Trypsin (AAT)
 - SERPINA1 gene, long arm 14q31-32.3, AR w/ codominant expression, 394aa, 52kDA, serine Protease inhibitor (Pi)
 - Produced by 1° hepatocytes 2° macrophages, renal tubules, small intestine epithelium and circulates in blood
 - Originally called “anti-trypsin” b/c the first known protease it inhibited was pancreatic trypsin but in fact it inhibits many proteases however pulmonary neutrophilic elastase is the principle protease it inhibits
 - various other “serinopathies” exist such as anti-thrombin (Thrombophilia), C1 inhibitor (Hereditary Angioedema), alpha1-antichymotrypsin (Familial Encephalopathy with Neuroserpin Inclusion Bodies)
- Mutation
 - Various point mutations can result in variable effects on the production/secretion/action of inhibitor
 - Alleles
 - To date over 100 alleles which vary based on level and activity of AAT however most are either of no clinical significance or extremely rare
 - Wild Type
 - M = wild type
 - Common Pathologic Alleles Among Caucasians (M/S/Z represents 95/2/1% of alleles, respectively)

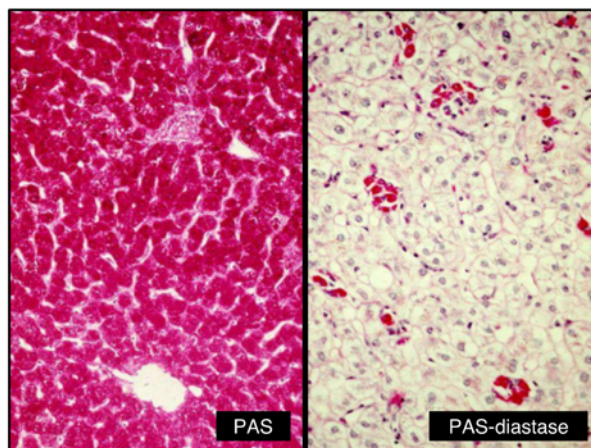
- S = single AA change (Glu264Val) ~0% polymerizes w/ 60% released into blood, and activity of this mutant AAT is 2x less than wild type hence mild pulmonary dz and little liver dz b/c there is very little polymerization unless in SZ dz where the Z stimulates the S polymers
- Z = single AA change (Glu342Lys), 85% polymerizes w/ 15% released into blood and activity of this mutant AAT is 5x less than wild type hence significant pulmonary dz and significant liver dz b/c lots of polymerization
- Rare Pathologic Alleles
 - N (Null) = no polymerization occurs and none is released into blood
 - Mmalton, Mduarte, et al = severely deficient level/activity
 - G, X, C, D, et al = relatively normal level/activity

Table 1. Diagnostic Tests for Alpha₁-Antitrypsin (AAT) Deficiency and Associated Disease Risks.*

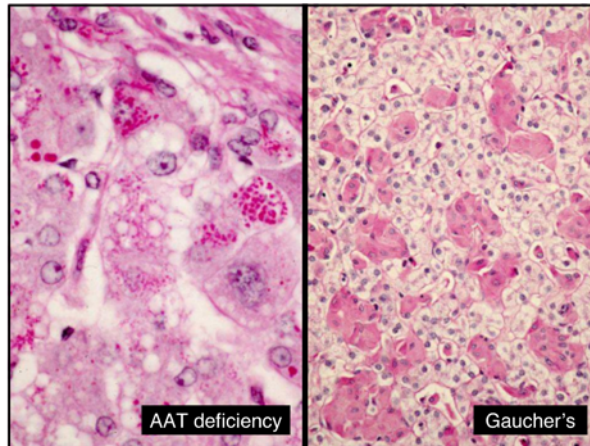
Inherited Genetic Variants†	Protein Phenotype‡	Serum Protein Level§	Molecular Genotype¶	Risk of COPD	Risk of Liver Disease
ZZ	Z	Very low	ZZ	Very high	High
ZNull	Z	Very low	Z/non-S, non-Z	Very high	Unknown
MZ	MZ	Intermediate	Z/non-S, non-Z	Possibly increased	Possibly increased
MNull	M	Intermediate	Non-S, non-Z/non-S, non-Z	Unknown	None
SZ	SZ	Low	SZ	Increased	Possibly increased
NullNull	None	None	Non-S, non-Z/non-S, non-Z	Very high	None

- Mechanism of Damage
 - Lung
 - Decreased activity and/or levels of AAT in the lung → uninhibited activity of neutrophilic elastase in pulmonary tissue (nl the ratio of elastase to AAT is 1:1) → as the lung is exposed to airborne pathogens there is constant activation of the immune system including neutrophil elastase which goes unchecked → destruction of pulmonary tissue
 - Liver
 - Only those alleles with pathologic polymerization → abnormal conformation and structural misfolding → formation of polymers that are (1) unable to be transported from RER to Golgi apparatus and (2) unable to properly destroyed → accumulation of polymers in hepatocytes → apoptosis
 - NB it is important to know that pts w/ the same pathologic genotype can still have variable liver disease b/c of variable intracellular degradation
 - Other Organs
 - the mechanism behind the rare disease of other organs is unclear, there is evidence that polymerization can occur outside of hepatocytes in extra-hepatic tissue (eg. skin Bx) and that these polymers themselves can actually induce inflammation
- S/S
 - In the adult population there is a long period b/t onset of Sx and Dx
 - Lung
 - variable representing the differences in exposure of pts to smoke or other inflammatory agents and other RFs including asthma, pneumonia, etc
 - Pediatric: NO Real Lung Disease
 - Adult: Emphysema ± Asthma and Bronchiectasis (but unclear), nl COPD S/S but there are some distinct features that should raise your suspicion for AAT: early onset (5th decade vs 6th decade), severe, non-smokers, predominant basilar disease, pan-acinar, FHx of unexplained liver/lung dz
 - Liver
 - Seen specifically in PiZZ pts
 - variable representing the differences in the ability of pts to degrade intracellular AAT
 - Pediatric: p/w prolonged jaundice w/ hepatomegaly during first few months of life specifically characterized as neonatal hepatitis w/ cholestasis, course is variable from asymptomatic abnl LFTs (10%) to death from liver failure during early childhood (2%)
 - Adults: Abnl LFTs, Cirrhosis w/ increased r/o HCC (pts MAY have higher risk even w/o cirrhosis)
 - Derm
 - Relapsing Necrotizing Panniculitis
 - chronic/recurrent but very rare
 - Histology: early there is a neutrophilic influx into the lower reticular dermis → later the inflammation extends into subcutaneous tissue of fat w/ necrosis

- S/S: single/multiple warm tender erythematous plaques esp on proximal extremities/trunk → ulcerate draining an oily substance (NB in some instances an antecedent of trauma occurs)
 - Mech: unclear but thought to result from unopposed proteolysis of the skin and/or accumulation of AAT polymers in the skin
 - Tx: Dapsone 100mg/d x1mo or Doxycycline 200mg/d x3mo, steroids/immunosuppressants/colchicine/danazole are not helpful, some case reports noting that AAT augmentation is helpful given the potential mechanism
 - Other
 - Vasculopathies: cANCA-vasculitis, CNS and abdominal aorta aneurysms, fibromuscular dysplasia, et al
 - IBD: it is hypothesized that the decreased antiprotease activity promotes injury to the GI tract potentially leading to IBD however studies are very conflicting
 - Glomerulonephritis: membranoproliferative GN and IgA Nephropathy possibly 2/2 impaired removal of IC by Kupffer cells in the liver
 - Neuro: Peripheral Neuropathy, MS
- Diagnosis
 - Neonatal Screening is controversial however every pt w/ unexplained COPD or liver dz should be screened, if +Dx discuss testing relatives
 - Labs (some propose doing serum and genotype and if discordant then reflex phenotype otherwise if concordant results then you have your answer)
 - 1st: Serum [AAT] <50mg/dL (nl range 70-104mg/dL) is insufficient to protect the lungs (typically seen in ZZ and ZN, MZ or MN pts are around 50-100 and if there is another liver injury like HCV then they can develop significant liver dz)
 - NB normal levels do not rule out dz b/c AAT is an APR and thus can be increased in states of stress, injury, inflammation, neoplasia, pregnancy (therefore measure concurrent ESR and CRP)
 - NB you can also get low levels w/ protein losing enteropathies or liver synthetic dysfunction
 - NB heterozygotes can have near normal levels but still be at increased risk
 - 2nd: Phenotype classified via the variable migration upon isoelectric focusing on polyacrylamide gel electrophoresis, very time intensive and technically challenging hence used as a reflex test
 - NB cannot distinguish b/t heterozygous (Pi*M) vs homozygous (Pi**) pathologic allele
 - NB "slow" alleles are named after M (eg. S, Z) while "fast" alleles are named before M (eg. A, L)
 - Genotype via PCR
 - NB in rare cases there is a discordance b/t serum level and genotype
 - NB does not test for some of the more rare alleles
 - NB PiMN genotypes will appear normal
 - PFTs/HRCT/Bx
 - LFTs/MRI/Bx
 - Bx: not necessary but often performed during initial workup of cryptogenic cirrhosis, infancy (bile duct paucity, intracellular cholestasis, giant cell transformation, mild inflammation, mild steatosis) → adult ("diastase resistant globules" aka inclusion bodies representing misfolded ATT w/in hepatocytes that stain to periodic acid-Schiff (PAS) even after Tx w/ diastase)
 - NB IHC w/ monoclonal Ab to AAT can be used to confirm dx
 - NB as dz of the liver worsens to cirrhosis these changes can resolve completely



- When stain w/ PAS all the carbohydrates are stained (left) but when you add diastase the glycogen stain is removed highlighting pathologic carbohydrates (right) like A1AT, Gaucher's, etc

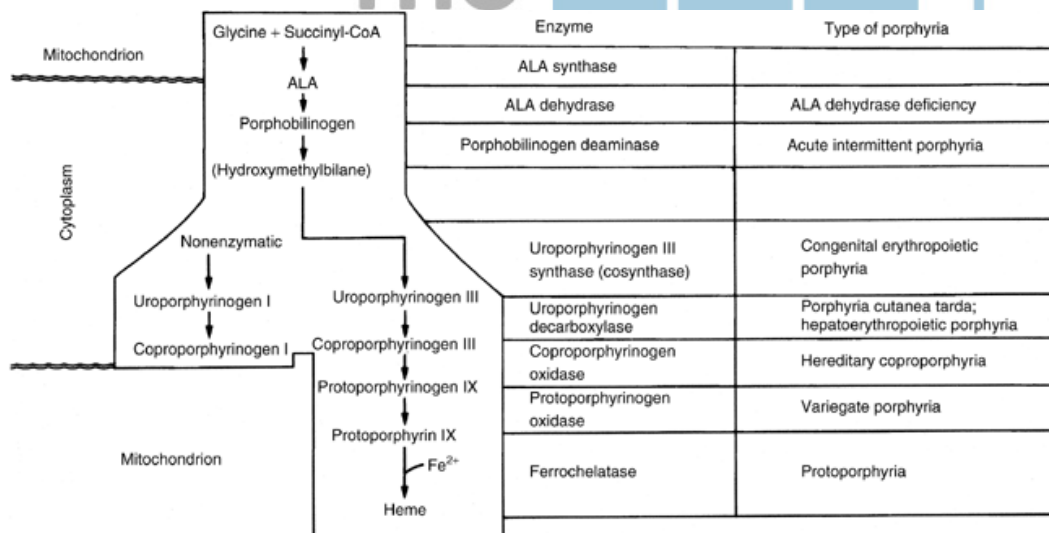


- Prognosis
 - Most studies looked at the PiZZ genotype
 - During the first few decades liver dysfunction is the major threat to life
 - After the first few decades lung dysfunction is the major threat to life
 - Overall survival is variable depending on the genotype and other concurrent pulmonary/liver injury
 - Mean life expectancy of PiZZ or PiSS is 48 or 52 yrs for smokers and 60 or 68 yrs for non-smokers
 - 2yr mortality is clearly related to decline in FEV1
- Treatment
 - Cirrhosis
 - Standard
 - Prevention: avoid alcohol and other hepatotoxins, aggressive management of metabolic syndrome, HAV/HBV vaccination
 - Typical cirrhosis Tx if present
 - Liver Transplant (3yr survival is 85%)
 - Aggressively screen for HCC w/ imaging (US/MRI) and labs (AFP)
 - Novel
 - Chaperon (eg. betaine, trimethylamine oxide, sarcosine, 4-phenylbutyrate) are being developed which inhibit polymerization by stabilizing monomers
 - Ribozymes are being engineered to target the destruction of mutant ATT RNA
 - Stimulate autophagy via inhibition of mTor pathways (eg. Sirolimus) vs independent mTor pathways (carbamazepine, valproic acid)
 - Stimulators (eg. Phenylbutyric Acid) enhances protein secretion Cyclosporine has been shown to reduce injury to hepatocytes
 - Similar therapeutics are being studied in other disease of inclusion like Huntington's and Parkinson's
 - Emphysema
 - Standard
 - Preventative: avoid smoking and other pulmonary irritants, pneumococcal/influenza vaccination
 - COPD Tx (meds, cardiopulmonary rehab, et al)
 - Lung Transplant
 - Acute infections are particularly damaging as it recruits more neutrophils therefore prompt abx Tx is imperative, studies show that frequency of infections correlates w/ decline in pulmonary function
 - The more aggressive use of steroids in mild COPD is controversial
 - Novel
 - A1AT Replacement Augmentation Therapy (Prolastin/Zemaira/Aralast)
 - weekly IV infusions at 60mg/kg over 15min
 - cost can range from \$60-150k/yr
 - derived from pooled purified human plasma
 - goal is to raise AAT levels to above protection threshold of 50mg/dL
 - other indications (FEV1 <80% of predicted but some advocate that if COPD is very severe the benefit of augmentation is negligible so some argue having a lower limit FEV1 of 30% of predicted, other rare high risk phenotypes, evidence of compliance, >18yo, non-smoker, pts w/ radiographic emphysema but nl FEV1 remains uncertain)
 - safe (several lots of Prolastin were pulled from the market when it was determined that the protein was derived from two pts w/ Creutzfeldt-Jacob Disease however there has

- been no reports of CJD developing in recipients) and well tolerated (only rare mild flu like illness) w/o significant SEs
 - o promising studies are looking at aerosolized AAT and recombinant AAT
 - o effectively increases AAT levels in not only serum but also epithelial lining fluid
 - o a multicenter prospective cohort study of 1129 pts by the NIH showed that statistical increase in survival and decrease in FEV1 decline in pts receiving augmentation therapy compared to those who did not, however definitive clinical efficacy has not been conclusively demonstrated by a DBRPCT
 - o it goes w/o saying that the replacement does NOT improve upon liver dsfxn
- gene therapy using adenovirus vectors targeting DNA transfer to airway tissue or peripheral skeletal muscle
- b/c AAT is an APR that releases to variety of stimuli pharmacologic strategies to increase endogenous AAT production AND release are being investigated especially since some mutant alleles still have a fair amount of anti-elastase activity

Porphyrrias

- Epidemiology
 - o History: Vampire/Werewolf Folklore, Insanity/Madness of King George III, Vlad III the Impale, Vincent van Gogh, King Nebuchadnezzar of Babylon
 - o "Porphyria" is Greek for purple pigment
- Mechanism
 - o Inherited or acquired (any liver dz but esp **hemochromatosis and HCV**, rheumatologic disorders, AIDS, heavy metal poisoning, benzene, etc, NB pts w/ liver dz develop porphyria b/c they are unable to clear metabolites) deficiency in the enzymes of the heme synthetic pathway (20% liver vs 80% bone) leading to insufficient production of heme but not clinically a problem b/c even deficient enzymes have enough activity to make enough heme rather it is the accumulation of porphyrins in various organs that is most important clinically b/c they are toxic at high levels
 - o Fractionated protoporphyrins



- Types (initially classified as either hepatic or erythropoietic b/c the two major sites of heme production was the liver and BM)
 - o **Acute Neurologic Porphyrias**
 - Types: 1° Acute Intermittent Porphyria (porphobilinogen deaminase), 2° Variegate Porphyria, Hereditary Coproporphyria
 - Mech: porphyrins act as pseudo-neurotransmitters
 - Diagnosis
 - elevated spot urinary AminoLevulinic Acid (ALA) and PorphoBilinoGen (PBG) (levels may be elevated only late in attacks, protect samples from light and preserved by refrigeration, consider psuedoporphyria when labs are negative)
 - after the diagnosis of porphyria is made then determine type by measuring various erythrocyte enzyme activities
 - Liver Bx: red fluorescence when exposed to UV light, needle like cytoplasmic inclusions, iron overload
 - S/S: dramatic life threatening Sx often precipitated by (refer below), more common in females
 - **Nervous System**

- Central: irritable, anxious, insomnia, personality changes → psychosis, seizures, AMS → coma
 - Motor: weakness
 - Sensory: dyesthesias/paresthesias
 - Autonomic
 - GI: lower quadrant colicky pain 2/2 autonomic dysfunction, constipation, N/V
 - CV: tachycardia, labile BP
 - Pulm: depressed respiration
 - Derm: sweating
 - GU: urinary retention
- Tx
 - IV hematin (Penhematin) 4mg/kg IV x4d decreases the drive for heme synthesis
 - nutrition w/ >400g of carbs, empiric antibiotics, IVF, propranolol autonomic effects, clonazepam for seizures
 - treat/avoid precipitating factor esp sun, alcohol, smoking, infection, menstrual cycle, fasting, medications (analgesics, anesthetics, AEDs, antimicrobials, anti-arrhythmics, diuretics, anti-hypertensives)
 - Tx of secondary causes (eg. HCV Tx)
 - if refractory then combined liver/BM transplant
- Chronic Cutaneous Porphyrrias
 - Types: 1° Porphyrria Cutanea Tarda (PCT) (uroporphyrinogen decarboxylase) (liver dz causes porphyria) 2° Erythropoietic Protoporphyrria (EPP) (porphyria causes liver dz)
 - Mech: porphyrins excite when exposed to 400nm light
 - Diagnosis
 - elevated spot urine/fecal/RBC uroporphyrin/protoporphyrin/coproporphyrin levels
 - S/S: subtle non-life threatening Sx
 - **Derm** (exact types depend on the type of chronic cutaneous porphyrias)
 - Photosensitivity w/ burning/stinging followed by erythema/edema (classic for EPP)
 - vesicles-bullae on sun-exposed skin after trauma esp on the dorsum of the hand, forehead, neck, ears (classic for PCT)
 - periorbital hypertrichosis
 - milia
 - sclerodermoid changes
 - porphyrins excreted in urine and cause urine to change from yellow to dark red when exposed to sunlight, brown teeth that fluoresce in ultraviolet light due to deposition of type one porphyrins
 - **Liver**: chronic cholestasis that eventually leads to cirrhosis in 5% of pts
 - Tx
 - Avoid 400nm wavelength light (this is not filtered by car glass, emitted by not only sun but also fluorescent light bulbs), alcohol, OCPs, iron
 - Phlebotomy (mainstay of Tx b/c removing iron somehow makes the disease quiescent)
 - Chloroquine and Vitamin E (forms complexes w/ porphyrins)
 - Tx of secondary causes (eg. HCV Tx)
 - If refractory then combined liver/BM transplant (NB phototoxicity from OR lights)