Hereditary Liver Diseases (Hemochromatosis is not invited to this party)

Nicole Kershner, MD
University of Louisville
Department of Gastroenterology, Hepatology, and Nutrition
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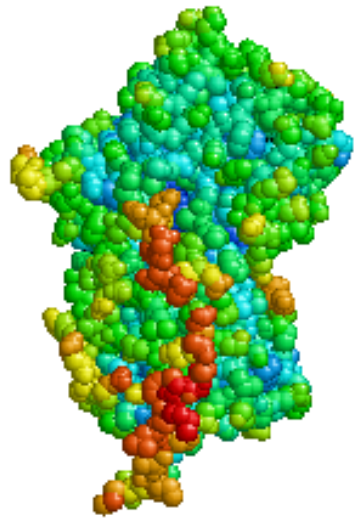
Overview

Inherited Hepatic Disorders

- α-1 antitrypsin Deficiency
- Wilson's Disease

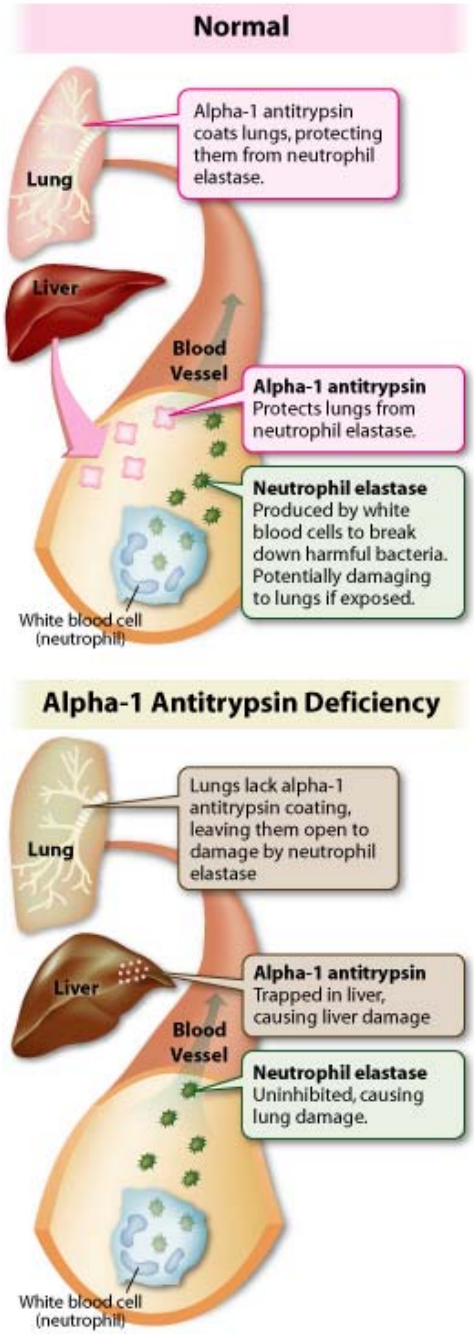
α-1 antitrypsin Deficiency

- Autosomal co-dominant disorder (prevalence 1 in 2,000-2,500 in the US)
- Gene is located on chromosome 14
- α-1 antitrypsin is a serum protease inhibitor (Pi) that is made in hepatocytes
- Z and M(Malton) allele are associated with liver disease
- PiMM = normal
- PiMZ =intermediate deficiency
- PiZZ = severe deficiency



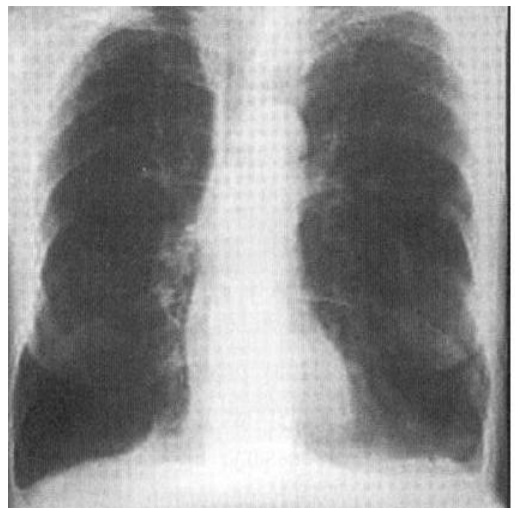
α-1 antitrypsin Deficiency Manifestations

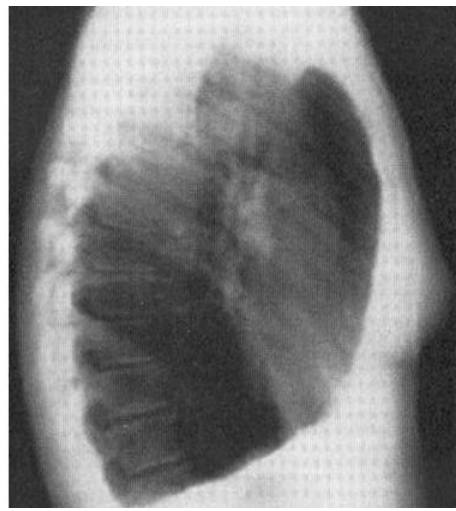
- Lung disease is caused from deficiency in serum α-1 antitrypsin.
- In contrast, liver disease relates to intrahepatic accumulation of α-1 antitrypsin molecules within the ER and decreased degradation of the Z-type molecule.



α-1 antitrypsin Deficiency Manifestations

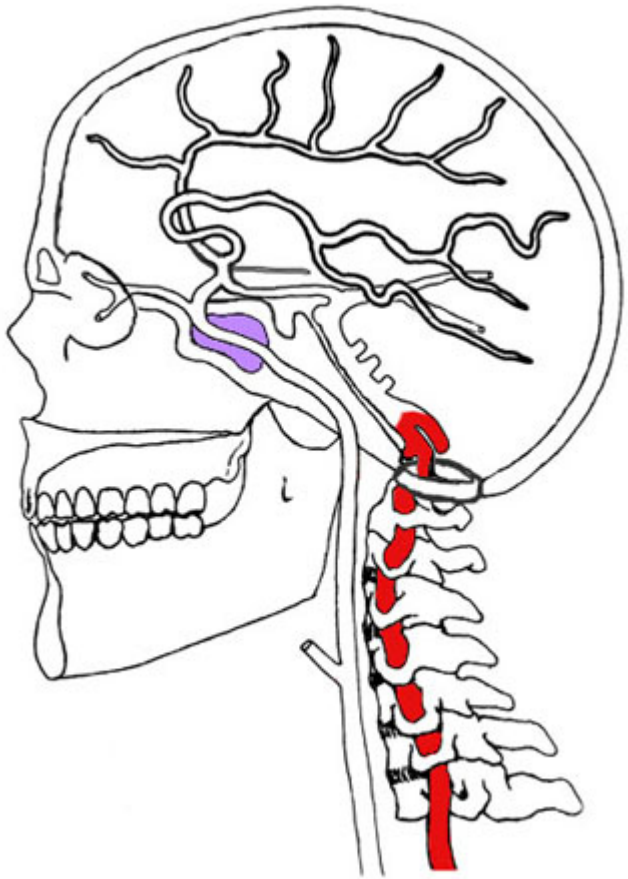
- Neonatal or childhood hepatitis/jaundice
- Adults with early onset emphysema (age <40 in smokers and at age <60 in non-smokers) and liver disease (cirrhosis, chronic active hepatitis, HCC)

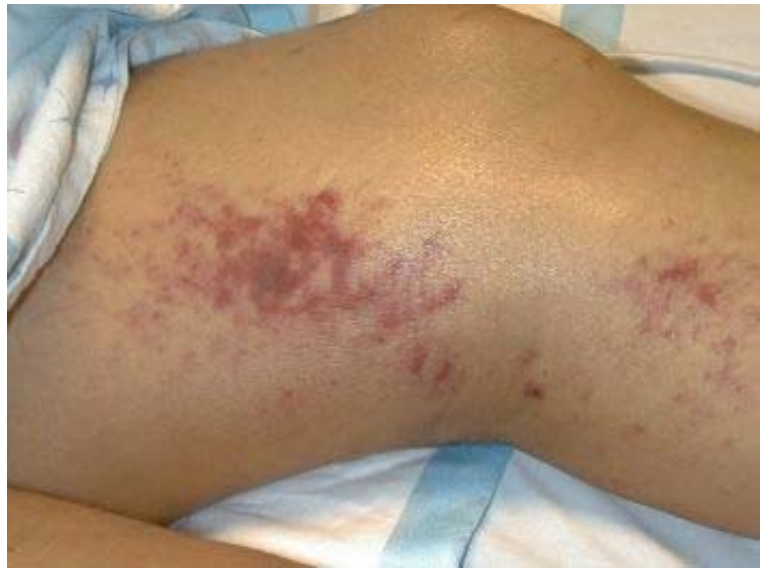




α-1 antitrypsin Deficiency Manifestations

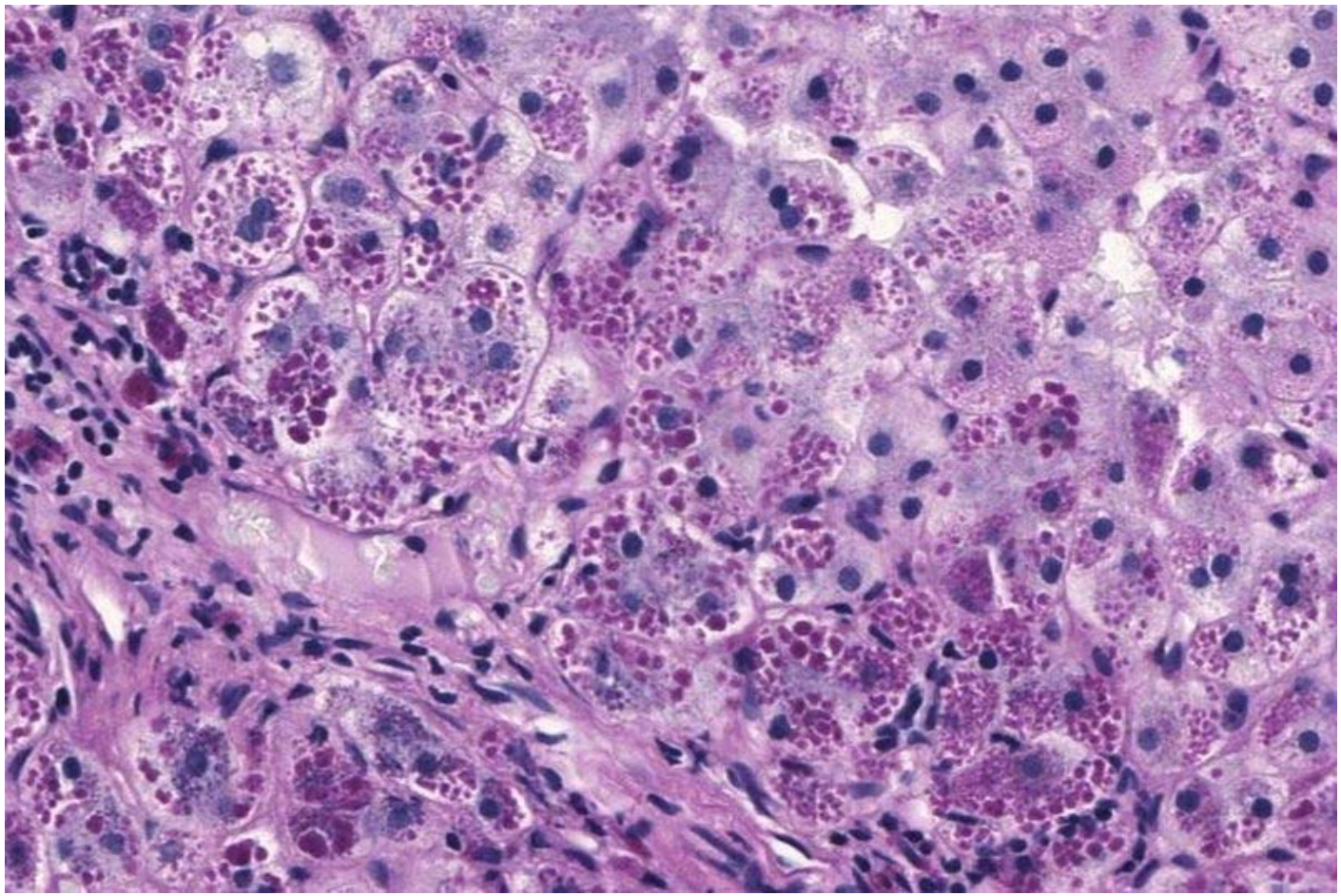
- Panniculitis





- Arterial aneurysms

α-1 antitrypsin Deficiency Pathology



α-1 antitrypsin Deficiency Diagnosis

- Serum protein electrophoresis and low serum α-1 antitrypsin (may be low/normal in acute illness)
- Confirmation must be made by phenotyping

α-1 antitrypsin Deficiency Treatment

- PiMZ heterozygotes have a small increased risk of liver disease, check liver function at 1-2 year intervals
- Supportive treatment
- Avoid smoking and alcohol
- Serial ultrasound screening for HCC
- Liver transplant for ESLD
- Unfortunately replacement therapy

with recombinant plasma A1AT

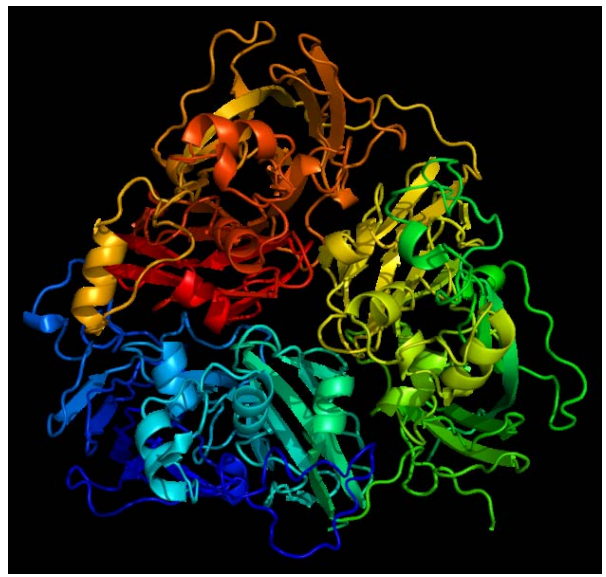
is not indicated for liver disease

Wilson's Disease

- Autosomal recessive (prevalence is 1 in 30,000)
- Mutation of ATP7B (Chromosome 13) gene which encodes copper-transporting P-type ATPase in hepatocytes causing a decreased hepatocyte excretion of copper in bile and decreased ceruloplasmin, leading to systemic copper accumulation
- Excess copper acts as a pro-oxidant and promotes the generation of free radicals leading to hepatocyte injury

Wilson's Disease

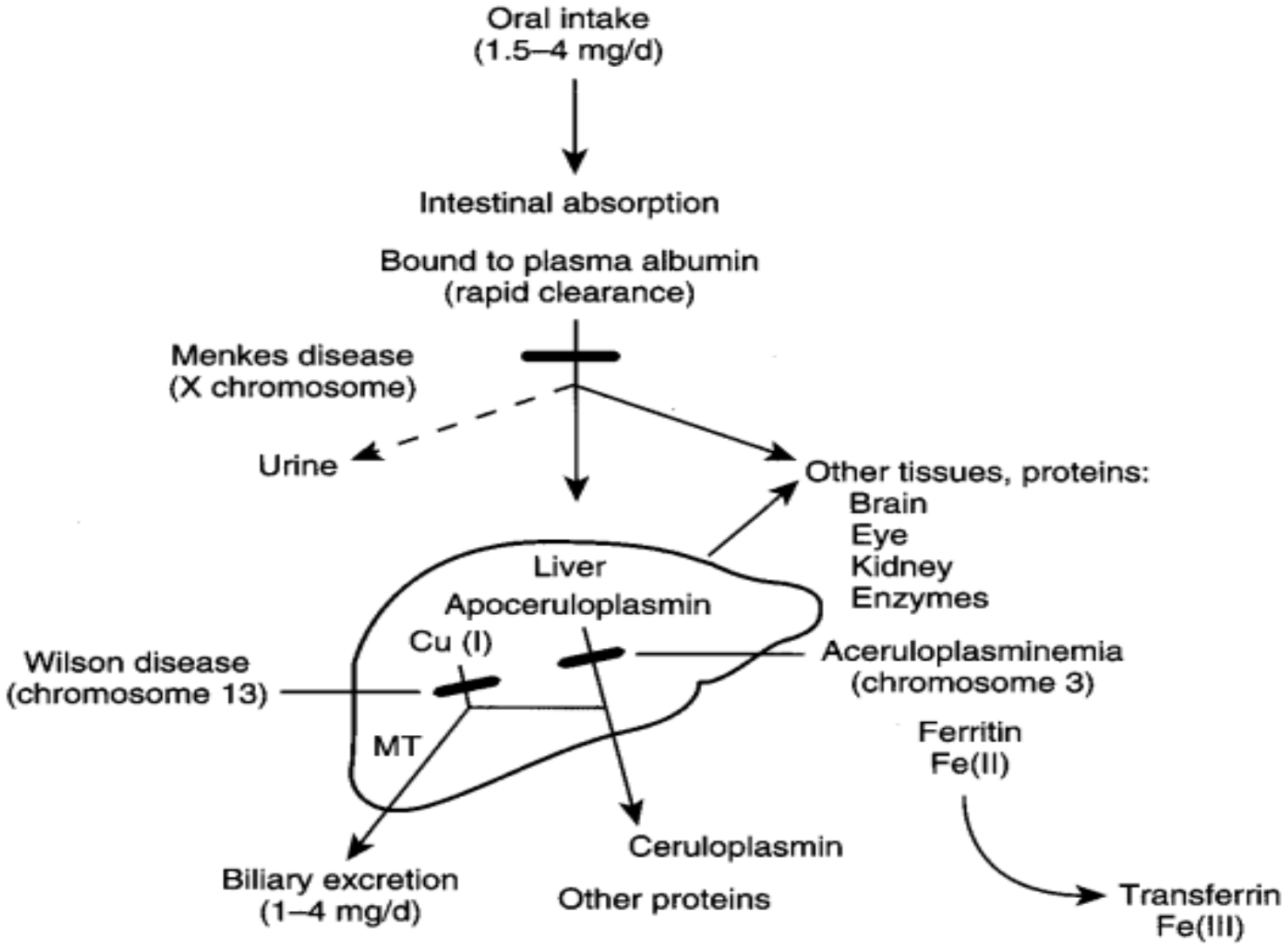
- Ceruloplasmin is the major copper-carrying protein in the blood
- Metallothionein (MT) is a protein that binds excess copper and once capacity is exceeded, copper is deposited in liver lysosomes = hepatic dysfunction



Wilson's Disease

- Increased hepatic copper content leads to copper leaking out of damaged hepatocytes and into the blood stream, causing an elevation in free serum copper concentration (and reduced ceruloplasmin)
- This presumably leads to copper deposition in the brain and other tissues

Copper Physiology



Feldman: Sleisenger & Fordtran Gastrointestinal and Liver Diseases, 7th Ed

Wilson's Disease

- Widely variable presentation
- Most common age of hepatic manifestations is 8-18 years of age
- Cirrhosis may be present in children below the age of 5
- May present as chronic liver disease in patients in their 50s and 60s

Wilson's Disease Manifestations

- Liver:

Hepatomegaly, splenomegaly (secondary to portal HTN), elevated ALT or AST, fatty liver, acute hepatitis or chronic hepatitis, AI-like hepatitis (arthropathy, rashes, fatigue, increased serum Ig, positive ANA and ASMA), cirrhosis, fulminant hepatic failure

Wilson's Disease Manifestations

- Neuro-psych:

Movement disorder, dysarthria, dystonia, ataxia, seizures, migraines, drooling, insomnia, tremors,

slurring of speech,

uncontrollable and

inappropriate grinning,

depression, psychosis,

personality changes

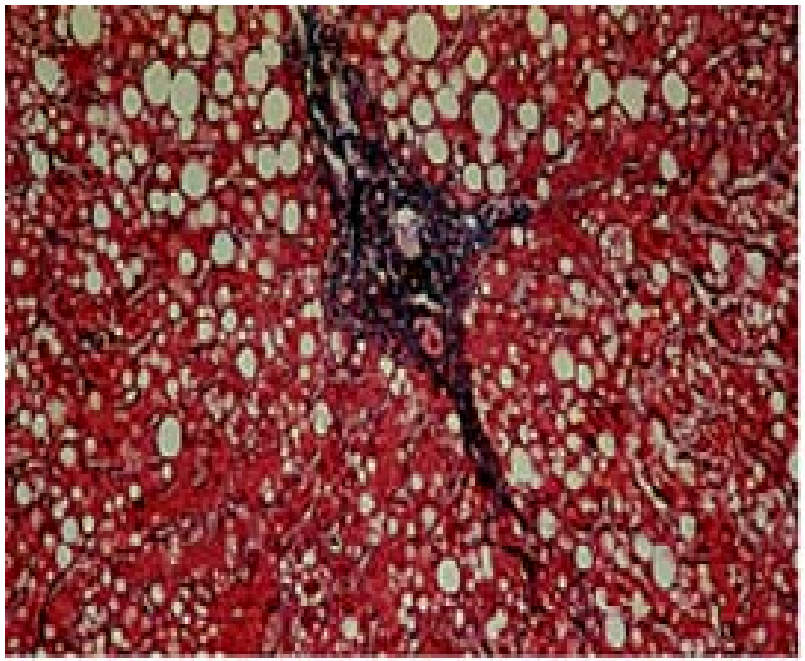
Wilson's Disease Manifestations

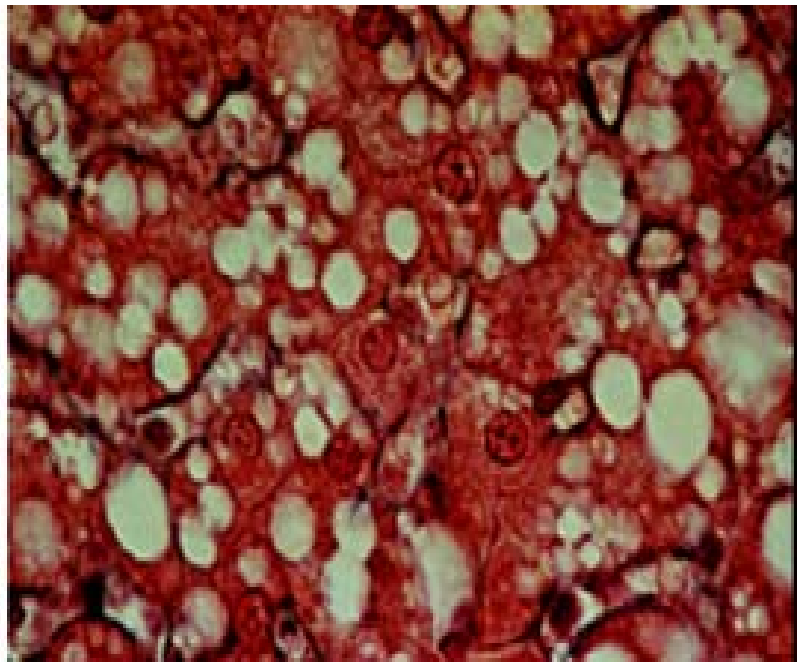
- Miscellaneous:

Renal stones (secondary to renal tubular acidosis), hemolysis, osteoporosis, cardiomyopathy, Fanconi syndrome, pancreatitis, hypoparathyroidism, dysrhythmia, miscarriages, menstrual irregularities, infertility

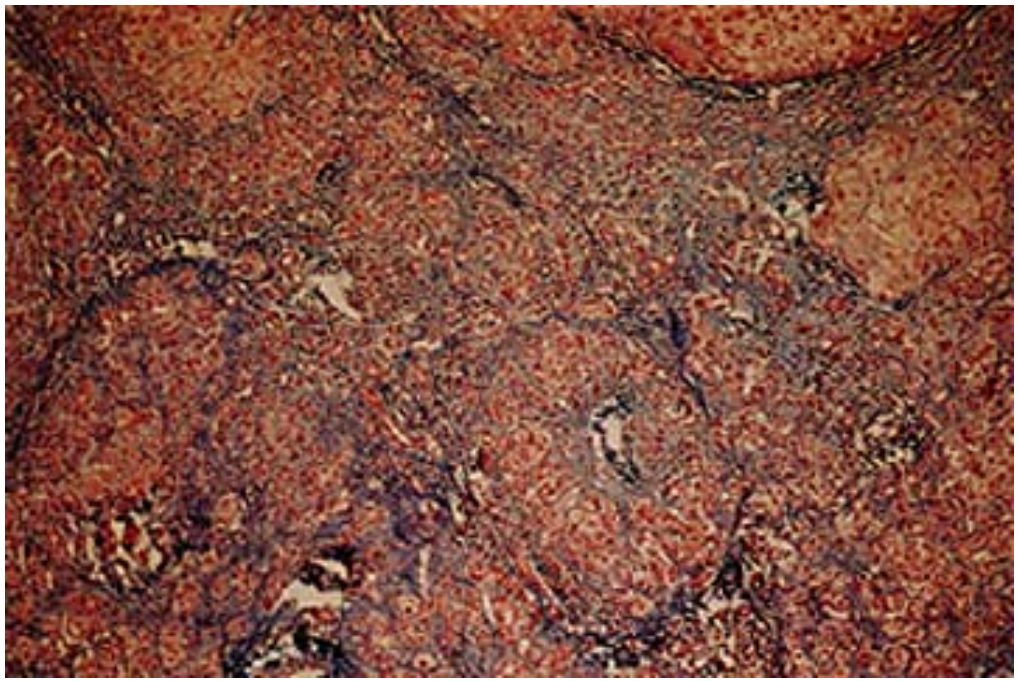
Wilson's Disease Pathology

- Earliest change is fatty infiltration in hepatocytes and glycogen inclusions within nuclei and portal fibrosis





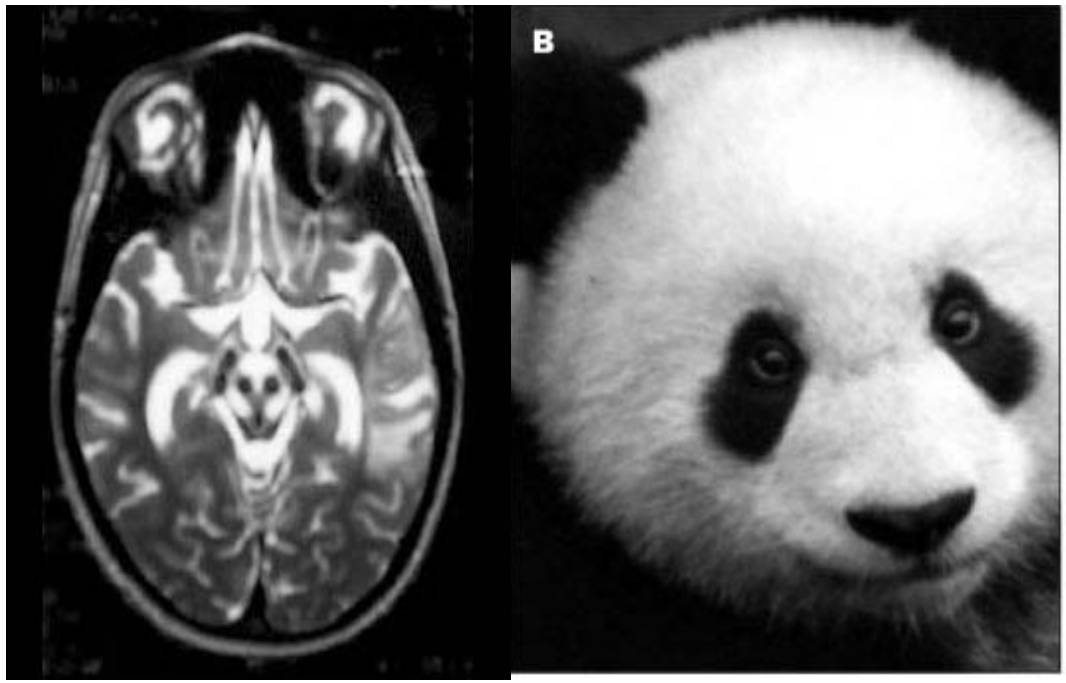
Wilson's Disease Pathology



- Progression of disease causes portal inflammation and fibrosis, piecemeal necrosis, and periportal hepatocyte necrosis, ultimately leading to cirrhosis

Wilson's Disease Diagnosis

- Ceruloplasmin level (<20mg/dL)
- MRI Brain (may see basal ganglia hyperintesity)



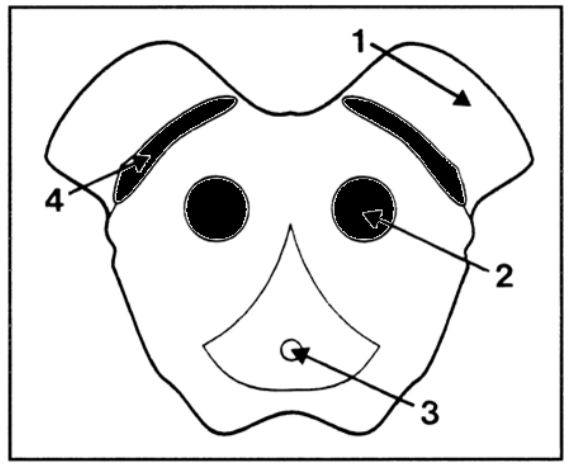
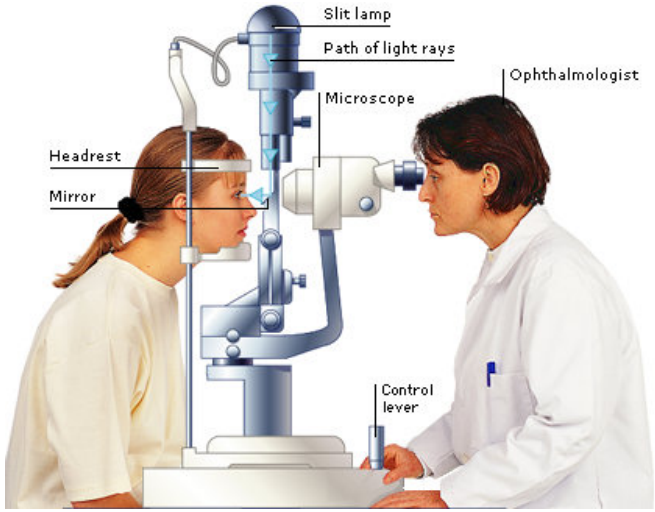


Fig 2. Midbrian aspect in a T2 weigthed RM scan as a result of to [?] normal signal at the red nuclei (eyes) and lateral aspects of the substantia nigra (ears), high signal at the tegmentum and hypointense superior colliculi [A]. Notice the resemblance to a panda [B].

Wilson's Disease Diagnosis

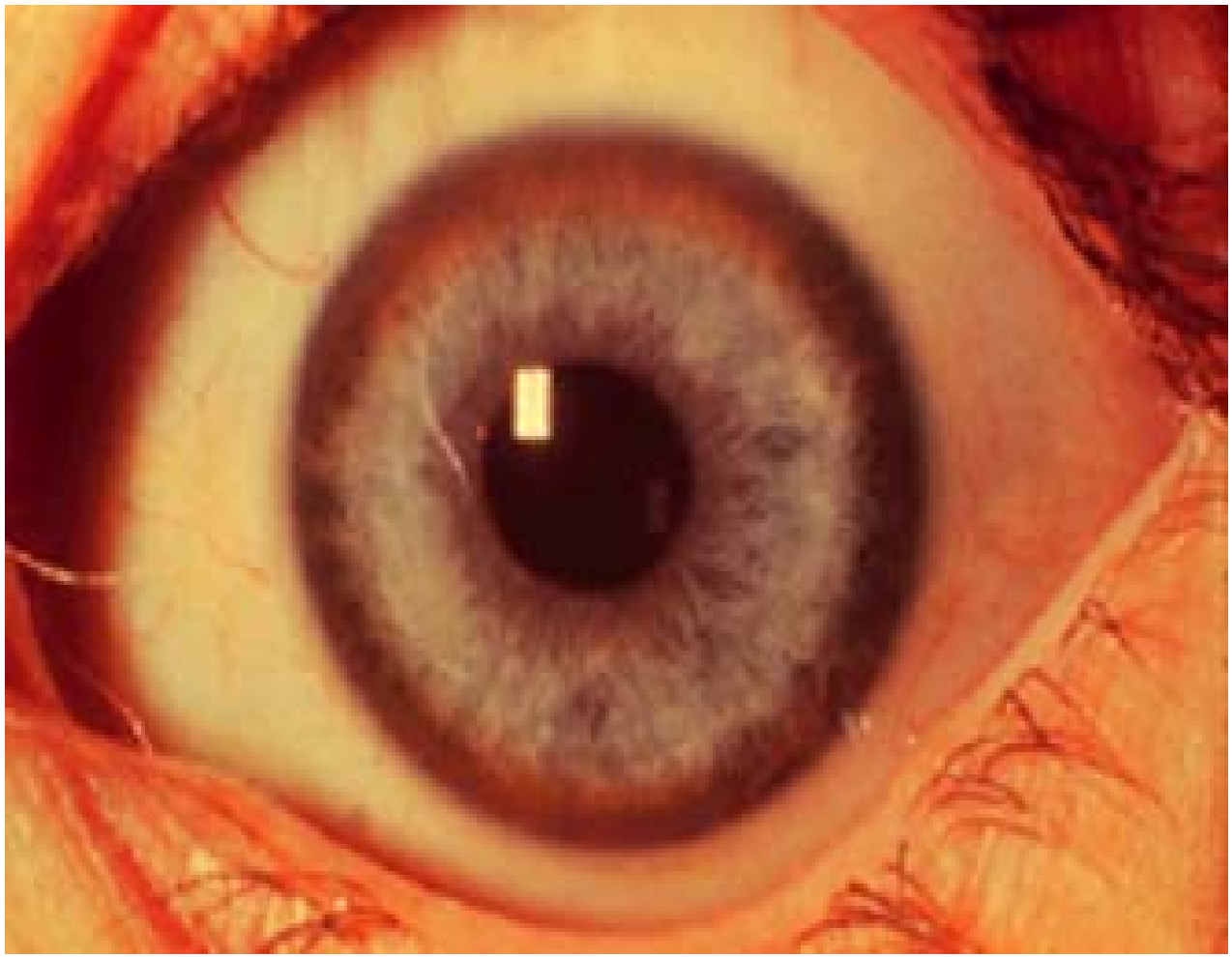
- Slit-lamp exam for Kayser-Fleischer rings
- 24 hour urine copper
- Liver biopsy with copper quant

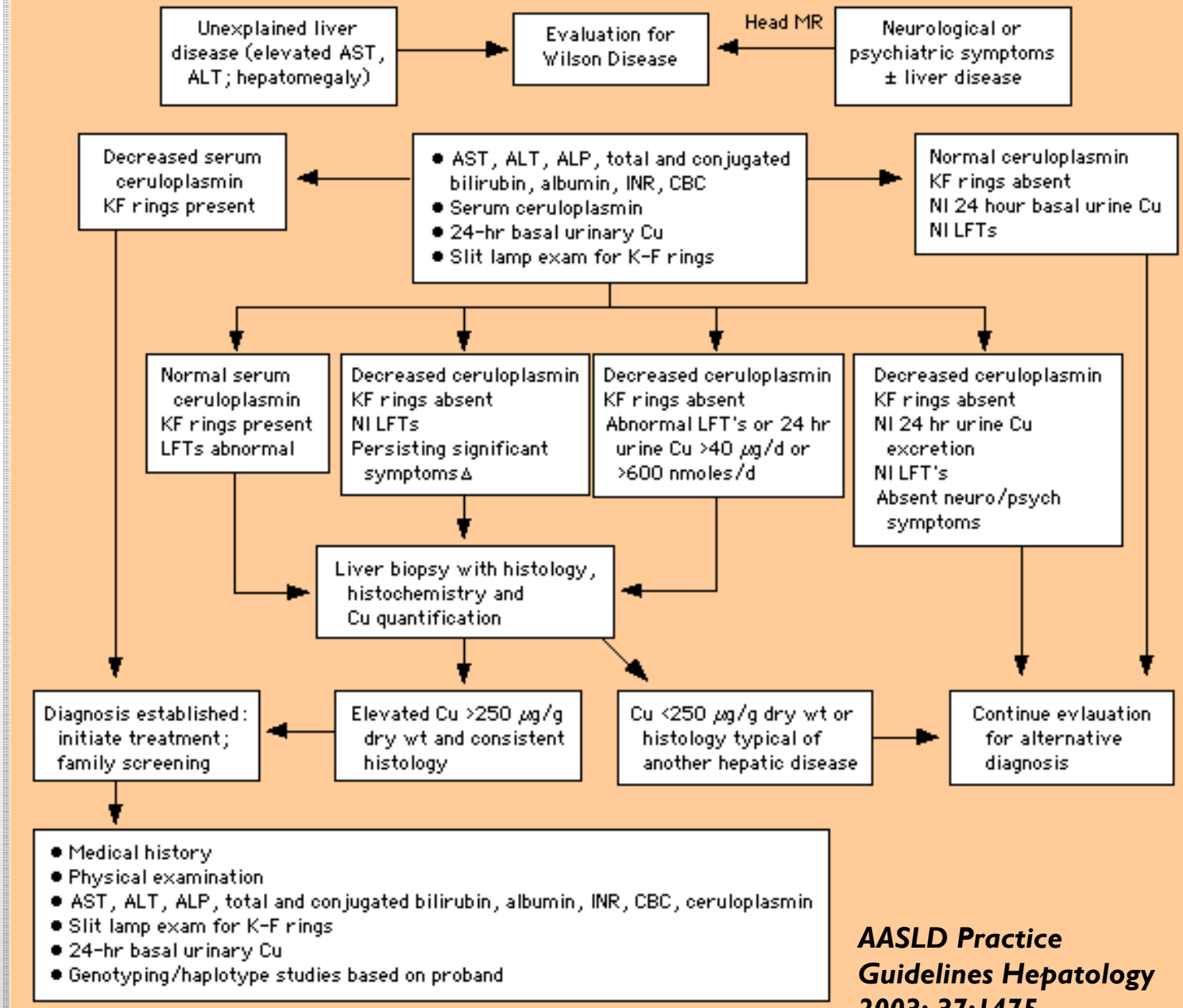


Wilson's Disease Diagnosis

- The low ceruloplasmin is due to failure to incorporate copper into ceruloplasmin → forming apoceruloplasmin (protein lacking copper)
- Ceruloplasmin is elevated by acute inflammation, pregnancy, and estrogens.
- Ceruloplasmin <5 mg/dL STRONGLY suggests Wilson's Disease. Normal ceruloplasmin does not exclude Wilson's Disease

Wilson's Disease
Kayser-Fleischer (KF) Rings





AASLD Practice Guidelines Hepatology 2003; 37:1475

* For patients under 18 years, a penicillamine challenge test may be performed prior to liver biopsy.
△ Persisting significant symptoms include: hemolysis, unexplained splenomegaly, extrahepatic manifestations of WD (see Table 2), and neurologic or psychiatric disorders.

Wilson's Disease

Diagnosis is confirmed by:

- Low ceruloplasmin and KF rings
- Liver biopsy with hepatic copper > 250 µg/g dry weight (normal is <50 µg/g dry weight) May have false negative in cirrhotic liver (uneven copper distribution), massive release of copper from necrotic hepatocytes in FHF. May have false positive in patients with chronic cholestasis.
- 24 hour urine Cu >40 mcg/day
- Direct mutation analysis (whole-gene sequencing) for ATP7B mutation in first degree relative in a confirmed patient

Wilson's Disease Screening

- Screen siblings of patients with Wilson's Disease is mandatory
  - Physical exam - Serum copper and ceruloplasmin
  - LFTs
  - 24-hour urinary copper excretion
  - Slit-lamp examination

Wilson's Disease Treatment

- Goals of therapy are to maintain negative copper balance by:
  - Decrease intake of copper
  - Shunt copper from its usual metabolic pathway by chelation
  - Alter copper absorption via competition
  - Limit toxic effects of copper by supplying antioxidants

Wilson's Disease Treatment

Wilson's Disease Treatment

Penicillamine

- Promotes urinary copper excretion
- Dosing: 250mg daily x 4 days, then BID for 4 days, then 500mg BID an hour before meals along with Pyridoxine 50mg daily
- Adverse effects: proteinuria (may lead to nephrotic syndrome), thrombocytopenia, neutropenia, LAD, fever, neurologic symptoms
- Pregnancy: unclear safety, do not breastfeed and decrease dose by 50% in the third trimester

Wilson's Disease Treatment
Trientine

- Promotes urinary copper excretion with less side effects than D-penicillamine
- Dosing: 750-1500mg daily in two or three divided doses taken an hour before or two hours after meals
- Pregnancy: unclear safety, do not breastfeed and decrease dose by 50% in the third trimester

Wilson's Disease Treatment
Zinc

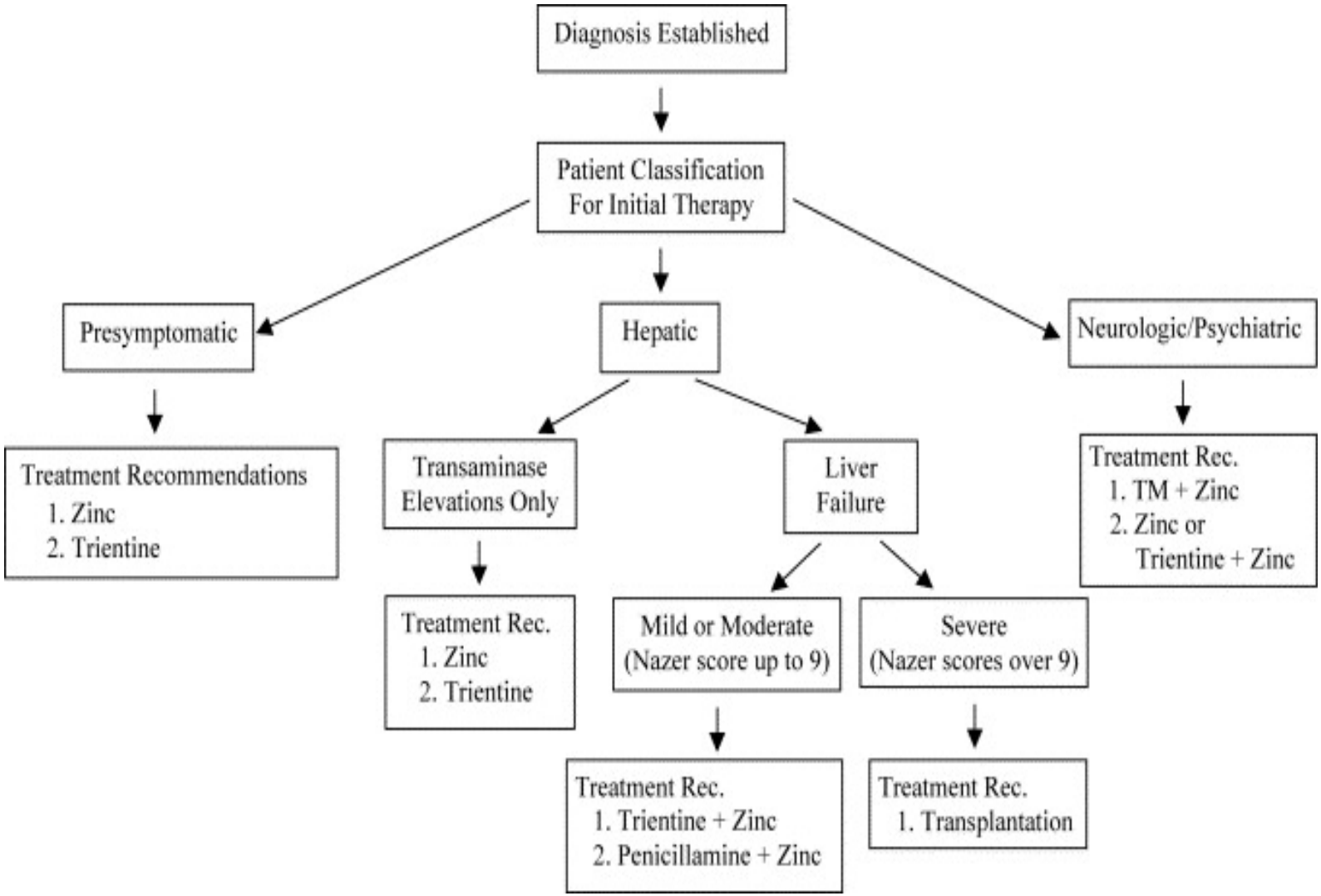
- Interferes with the intestinal absorption of copper and it also induces metallothionein (MT)
- Dosing: 50mg TID (5 hours away from chelators) on a fasting stomach

Wilson's Disease Treatment

Tetrathiomolibdate

- Interferes with copper absorption and binds to plasma copper
- More effective for neurological disease
- Unfortunately, not commercially available

Wilson's Disease Treatment



Brewer GJ, Askari FK, Journal of Hepatology 2005; 42 Suppl(1):S13-S21

WILSON's disease

The first step in evaluating patients presenting with hepatic decompensation is to establish disease severity, which can be estimated using the Nazer prognostic index (Table 354-3). Patients with scores <7 can usually be managed with medical therapy. Patients with scores >9 should be considered immediately for liver transplantation, and those with scores between 7 and 9 require clinical judgment as to whether to recommend transplantation or medical therapy. A combination of trientine and zinc has been used to treat patients with Nazer scores as high as 9, but such patients should be watched carefully for indications of hepatic deterioration, which mandates transplantation.

Table 354-3 Prognostic Index of Nazer

Laboratory Measurement		Score (in Points)				
	Normal Value	0	1	2	3	4
Serum bilirubin[a]	0.2–1.2 mg/dL	<5.8	5.8–8.8	8.8–11.7	11.7–17.5	>17.5
Serum aspartate transferase (AST)	10–35 IU/L	<100	100–150	151–200	201–300	>300
Prolongation of prothrombin time (seconds)	—	<4	4–8	9–12	13–20	>20

[a]If hemolysis is present, the serum bilirubin cannot be used as a measure of liver function until the hemolysis subsides.

Source: Modified from H Nazer et al: Wilson's disease: Clinical presentation and use of prognostic index. Gut 27:1377, 1986; with permission from BMJ Publishing Group.

Wilson's Disease Treatment

Zinc - Debate

Research by Weiss published in Gastroenterology in April 2011)

- Study was designed to assess long-term treatment outcomes and reasons for discontinuation of medical therapy for WD
- Discontinuation of therapy was seen more frequently in patients receiving zinc monotherapy or combination therapy than a chelation agent alone.
- This was unexpected because there is a known limitation to using penicillamine therapy due to occurrence of adverse events
- Also, treatment failure was observed more frequently with zinc monotherapy (assessing liver function enzymes)
- New concept of nonresponse with zinc therapy?

Wilson's Disease Treatment

Zinc

- Patients that had an insufficient hepatic response with zinc monotherapy underwent "rescue therapy" with change to chelator therapy.
- It was observed that liver enzyme levels normalized in zinc nonresponders after the introduction of a chelating agent.
- Compliance was not assessed in this study (therefore inadequate intake of zinc cannot be ruled out as a cofactor) but there was no difference in serum and urinary zinc levels between zinc responders and nonresponders
- Best response seen with combination therapy (very difficult due to strict and complex medication time schedules)

Wilson's Disease Monitoring Therapy

- Follow the 24 hour urine Cu (200-500 mcg/day) and "free serum Cu" (>15 mcg/dL = poor compliance, <5 mcg/dL = overtreatment)
- Fulminant hepatic failure? Rapid removal of copper and liver transplantation
- No recommendations on screening for hepatocellular carcinoma (unclear if there is an increased risk of malignancy)
- Lifelong compliance is essential

Resources

- *AASLD Practice Guidelines Hepatology*
- Brewer GJ, Askari FK, Journal of Hepatology 2005; 42 Suppl(1):S13-S21
- Brewer GJ, Yuzbasiyan-Gurkan V. Wilson's Disease. Medicine (Baltimore) 1992; 71:139
- Fairbanks KD, Tavill AS. Liver disease in alpha 1-antitrypsin deficiency: a review. Am J Gastroenterol 2008; 103:2136.
- Feldman: Sleisenger & Fordtran Gastrointestinal and Liver Diseases, 7th Ed
- Ferenci, P. Diagnosis and Current Therapy of Wilson's Disease. Alimentary Pharmacology & Therapeutics. 2004;19(2)
- Kenyon, AP, Girling, JC. Liver disease in pregnancy. Women's Health Medicine 2005; 2:26
- Schwarzenberg SJ, Sharp HL: 1-Antitrypsin deficiency, Chap 27, In Schiff L, Schiff ER (Eds): Diseases of the Liver 7th edition. Philadelphia, Pa, JB Lippincott, 1993, pg 692-706
- Weiss, K, Gotthardt, D, Klemm, D, et al. Zinc Monotherapy Is Not as Effective as Chelating Agents in Treatment of Wilson Disease. Gastroenterology, April 2011. Volume 140, Issue 4, 1189-1198