Hepatolenticular Degeneration

Ashutosh Barve, M.D., Ph.D.
Gastroenterology/Hepatology Fellow
University of Louisville

Case Presentation

- 17 year old caucasian woman with no previous medical history
- Presents with a 2-3 day history of right and left upper quadrant pain, abdominal distension and bilateral LE edema
- She also c/o fatigue for about 6 weeks along with subjective fevers and occasional headache

Case Presentation

- PHYSICAL EXAM:
  - Right upper quadrant tenderness
  - Slight abdominal distension
  - Soft abdomen with no hepatospleenomeg.
  - 2+ bilateral lower extremity edema
  - Normal cardio-respiratory exam
  - Normal neurological exam

Case Presentation

- INITIAL LABORATORY DATA:
  - Na=134, K= 3.4, Cl=107, CO2=23,
  - BUN=11, Cr=1.0
  - Hgb=11.4, Hct=33.4, Ptt=144, WBC=7.6
  - **AST=148, ALT=83**, AlkP=73, **TBil=1.6**
  - **Alb=2.5**, TProt=6.1
  - **PT=20.7**, PTT=45.5

Case Presentation

- RADIOLOGY:
  - Chest X-ray – normal
  - Abdominal US – moderate ascites, mild diffuse thickness of the gall bladder wall consistent with hepatitis, otherwise normal

- She was admitted with a provisional diagnosis of hepatitis vs. mononucleosis with hepatic involvement

Case Presentation

- FURTHER WORK UP:
  - Ferritin=231
  - ANA=neg, AMA=neg, ASMA=neg
  - Hepatitis profile=neg
  - Monospot test=neg
  - **Ceruloplasmin=13 mg/dL (normal 20-45)**

Case Presentation

- FURTHER WORK UP:
  - Slit lamp exam by Ophthalmology revealed Kayser-Fleischer rings
  - 24 hr urine copper = 3200 mcg/L (normal 5-30 mcg/L)
  - Liver Biopsy was done and samples sent for light and electron microscopy

Case Presentation

- Liver Biopsy:
  - Light Microscopy: “Chronic active hepatitis with early cirrhosis. A small amount of stainable copper is demonstrated….”

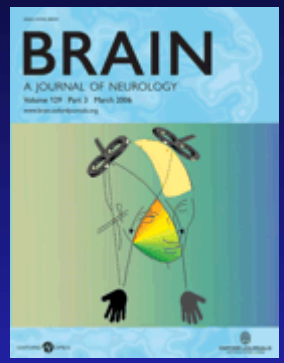
Case Presentation

- Liver biopsy:
  - Electron Microscopy: "….In some of the nuclei are found accumulations of glycogen particles….Many mitochondria are of giant size and bizarre shapes…In addition the **membranes of the cristae are widened forming small and large electron-lucent round swellings bordered by a single membrane**. Also noted in the mitochondria are various electron-dense granules….."

  Impression: Electron microscopy of this adequate liver biopsy is consistent with Wilson's disease

Samuel Alexander Kinnier Wilson

- Neurologist and Pathologist
- Born in New Jersey, USA
- Lived and worked in England
- Professor of Neurology at King's College Hospital
- Great clinician and teacher, proficient linguist, keen gardener and avid golfer



PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER.

WILSON SAK, *Brain.*1912; 34: 295-507.

Wilson Disease

- Autosomal recessive
- Prevalence of approximately 1 case in 30,000 live births in most populations
- Defect in hepatic copper transport leading to accumulation of copper in the liver
- Excess copper acts as a pro-oxidant and promotes the generation of free radicals leading to hepatocyte injury.

Synonyms of Wilson Disease

- Hepatolenticular Degeneration
- Progressive Lenticular Degeneration
- Kinnier Wilson's Disease
- Westphal-Strumpell's pseudosclerosis

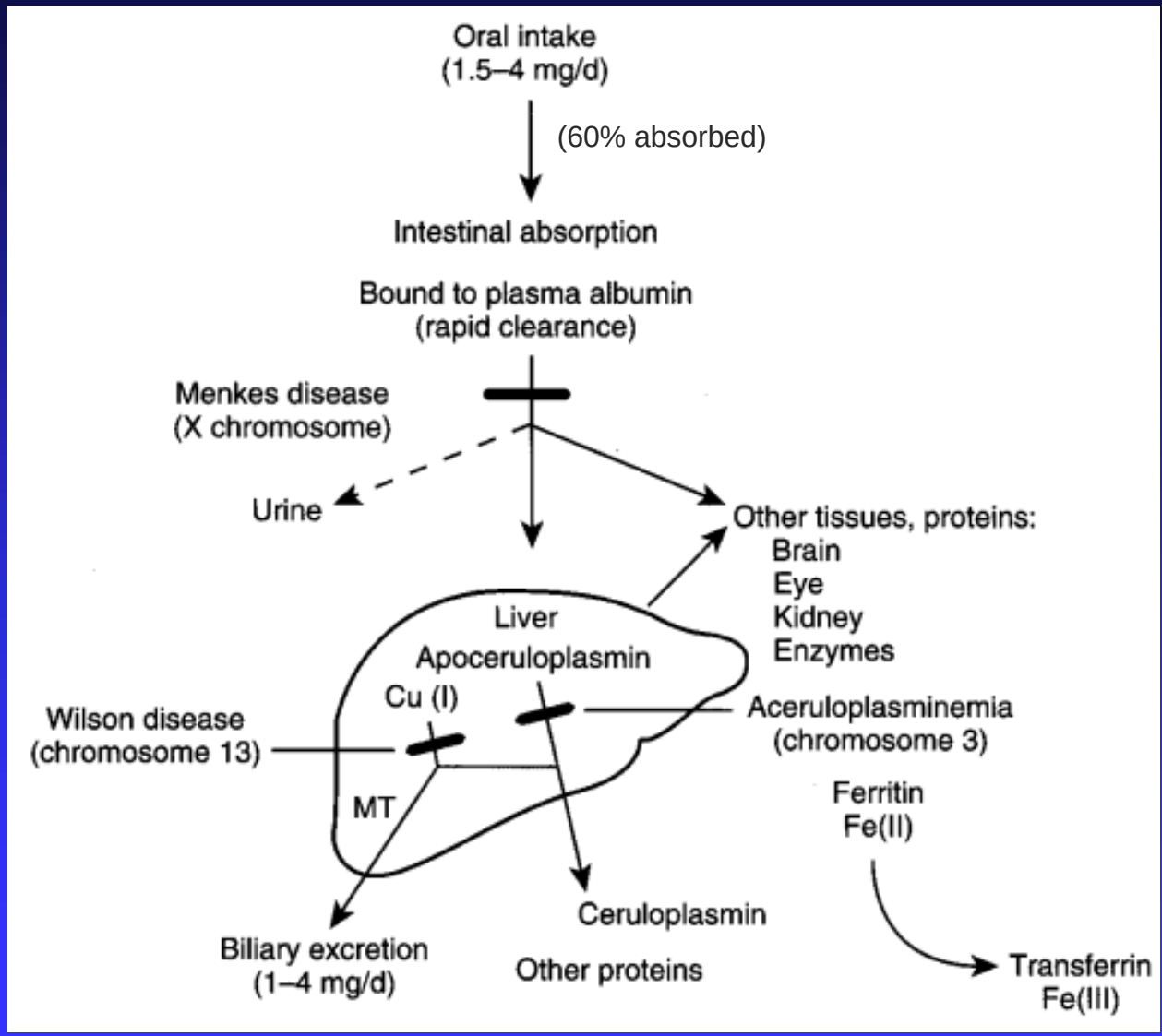
Historical Perspective

- 1860 – Frerichs describes a case similar to those described by Wilson
- 1912 – Wilson publishes his case series
- 1912 – Eye findings associated with WD described by Kayser and Fleischer
- 1929 – Vogt and Haurowitz & Glazebrook report excess copper in the brain and liver of WD patients

Historical Perspective

- 1936 – Policard et al demonstrate excess copper in the corneal KF ring
- 1956 – Bennetts and Chapman establish relationship between abnormal copper metabolism and WD
- 1952 – Sternlieb and Gitlin describe an almost universal low ceruloplasmin in WD
- 1993 – The gene that is abnormal in WD is identified (Nature Genetics)

Copper Physiology



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

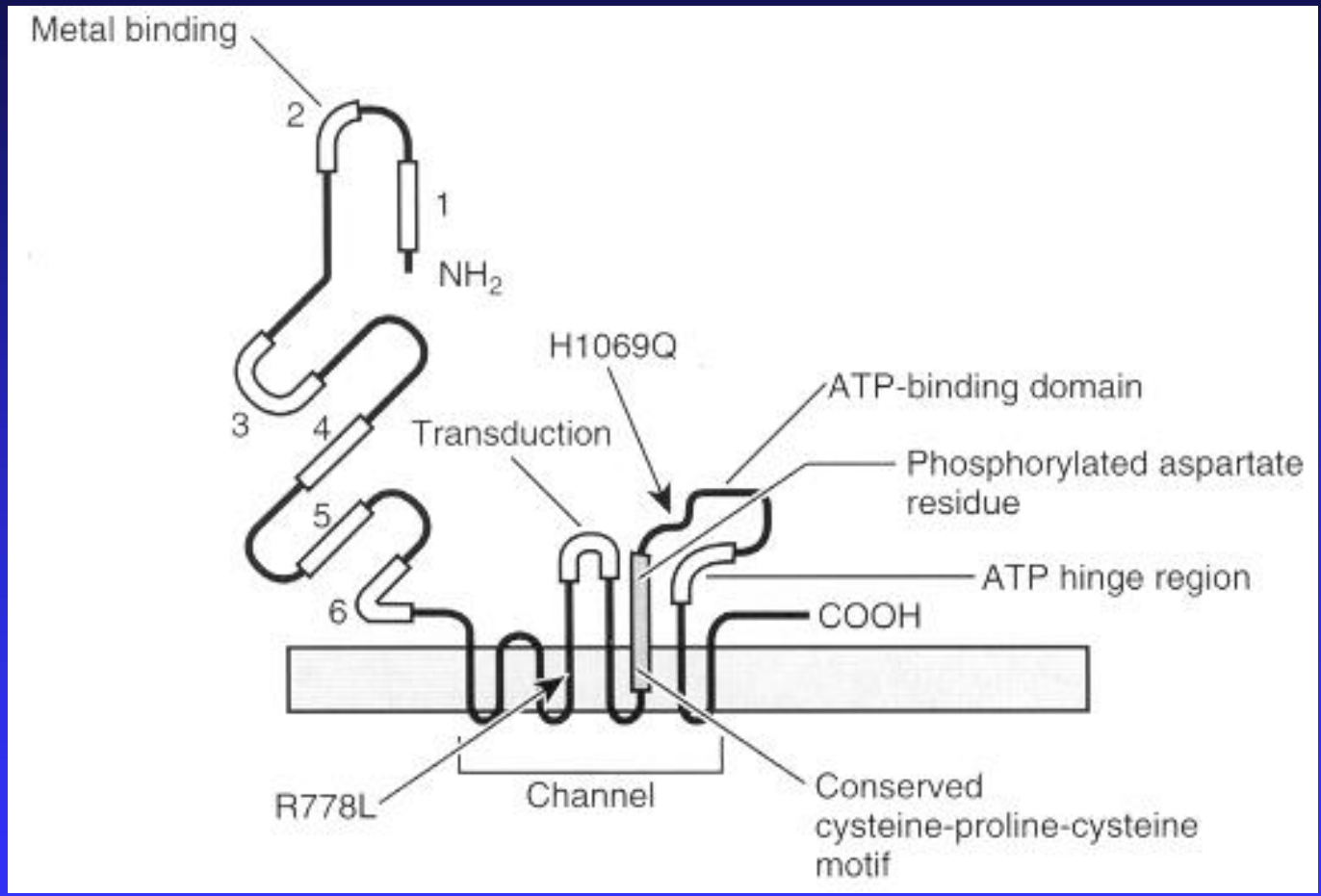
Diseases of Copper Transport

- Menkes' Disease:
  - X-linked genetic disorder
  - Defect in the transport of copper from the intestine, leading to copper deficiency
  - Results in death from severe progressive neurodegeneration
- Wilson Disease
  - Decreased transport of copper from the liver into bile, leading to copper excess

Diseases of Copper Transport

- Menke's Disease:
  - X-linked disorder
  - Gene product is ATP7A
- Wilson's Disease
  - Genetic defect localized to Chromosome 13
  - Gene product is ATP7B – high degree of homology with ATP7A

ATP7B Gene Product

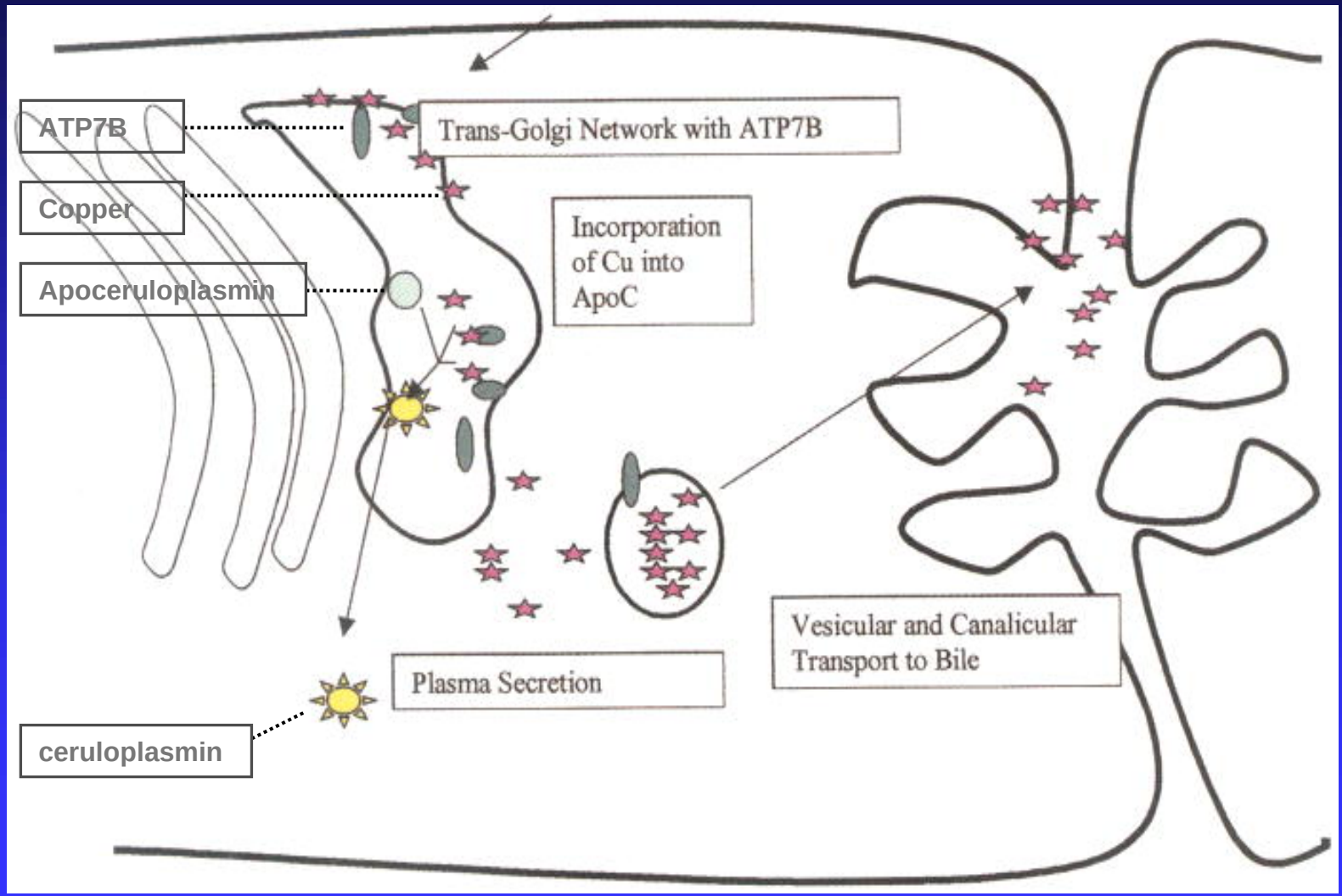


P-Type ATPase

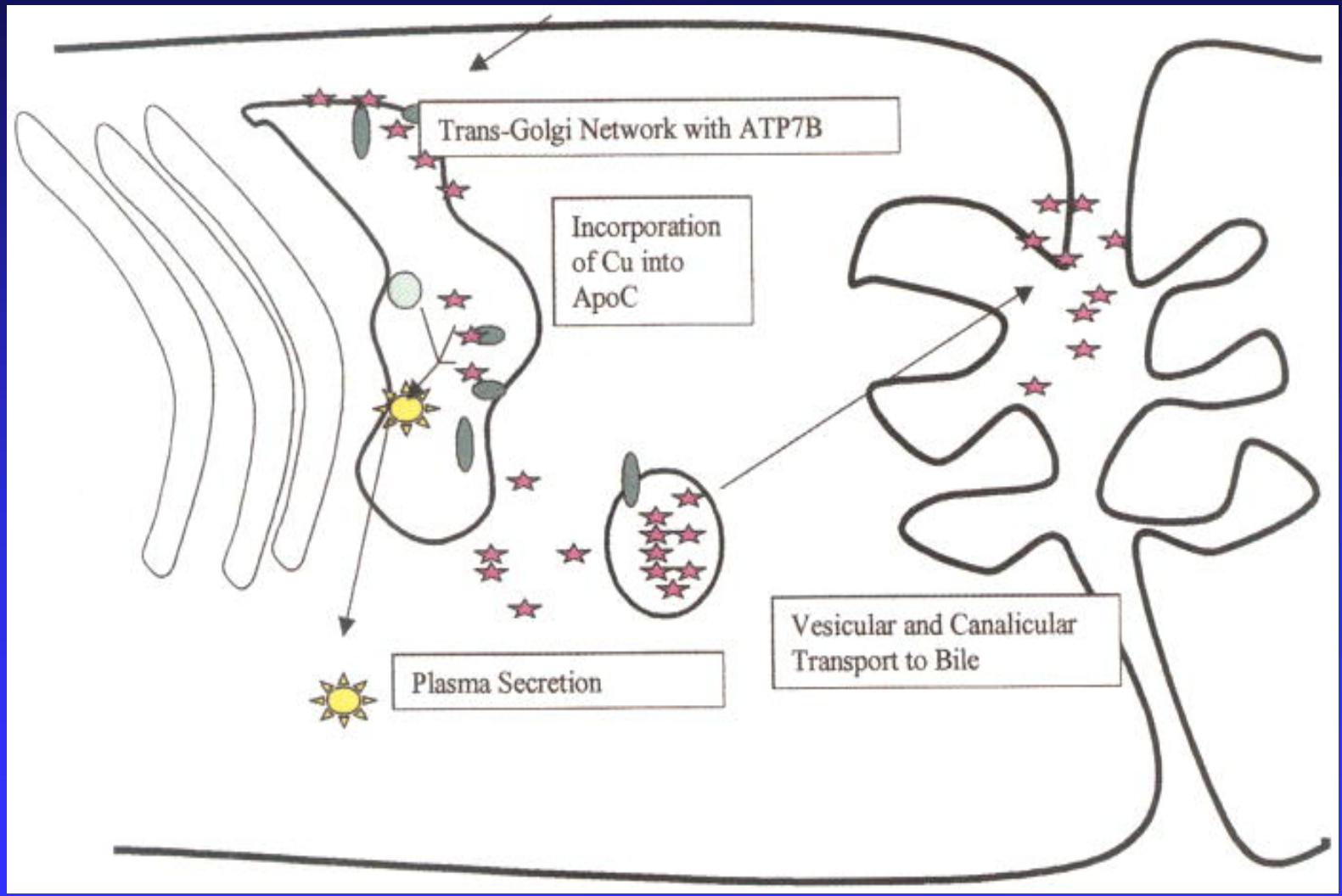
1443 amino acids, 6 copper-binding motifs, 1 ATP binding region

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

Hepatocyte Copper Transport



Hepatocyte Copper Transport

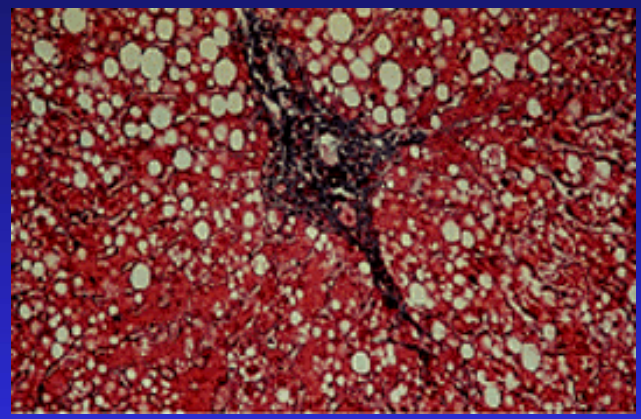


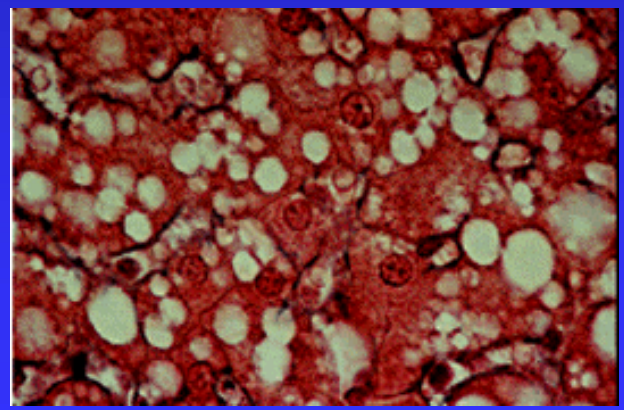
Genetic Basis of Wilson’s Disease

- More than 100 mutations in the gene have already been identified in patients with Wilson's disease
- Most patients are compound heterozygotes
- Histidine1069Glutamine mutation is one of the most frequent mutation with an allelic frequency of 10 to 40 percent

Pathology

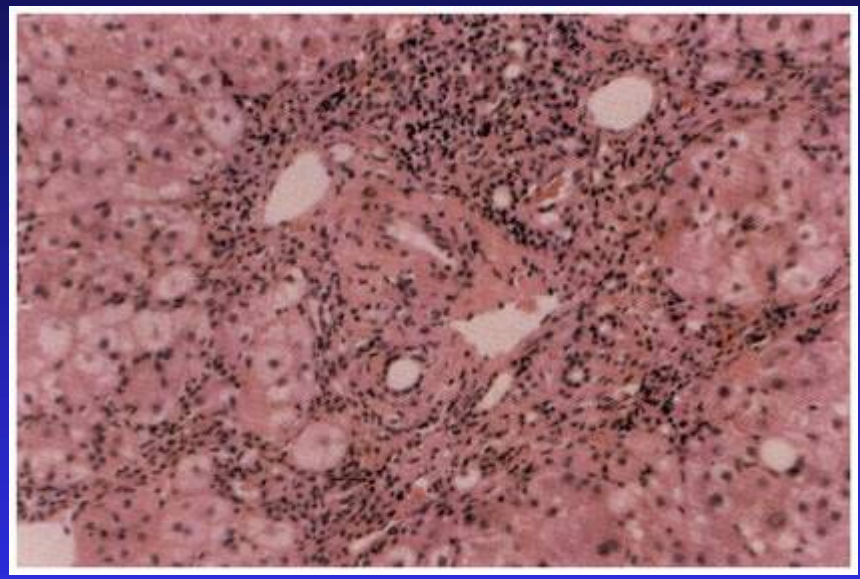
Earliest lesion in Wilson Disease is **fatty infiltration** within hepatocytes, glycogen inclusions within nuclei, and portal fibrosis





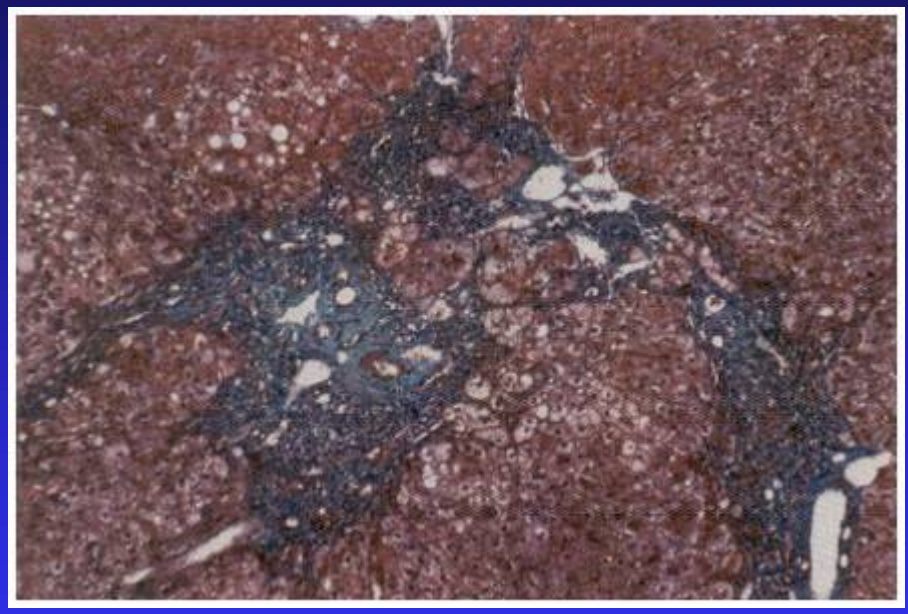
Pathology

- As the disease progresses the histologic lesion resembles that of **Autoimmune Chronic Hepatitis**



- There is portal inflammation and fibrosis, piecemeal necrosis, with marked swelling and necrosis of periportal hepatocytes

Pathology



Ultimately the inflammation and fibrosis leads to **Cirrhosis**

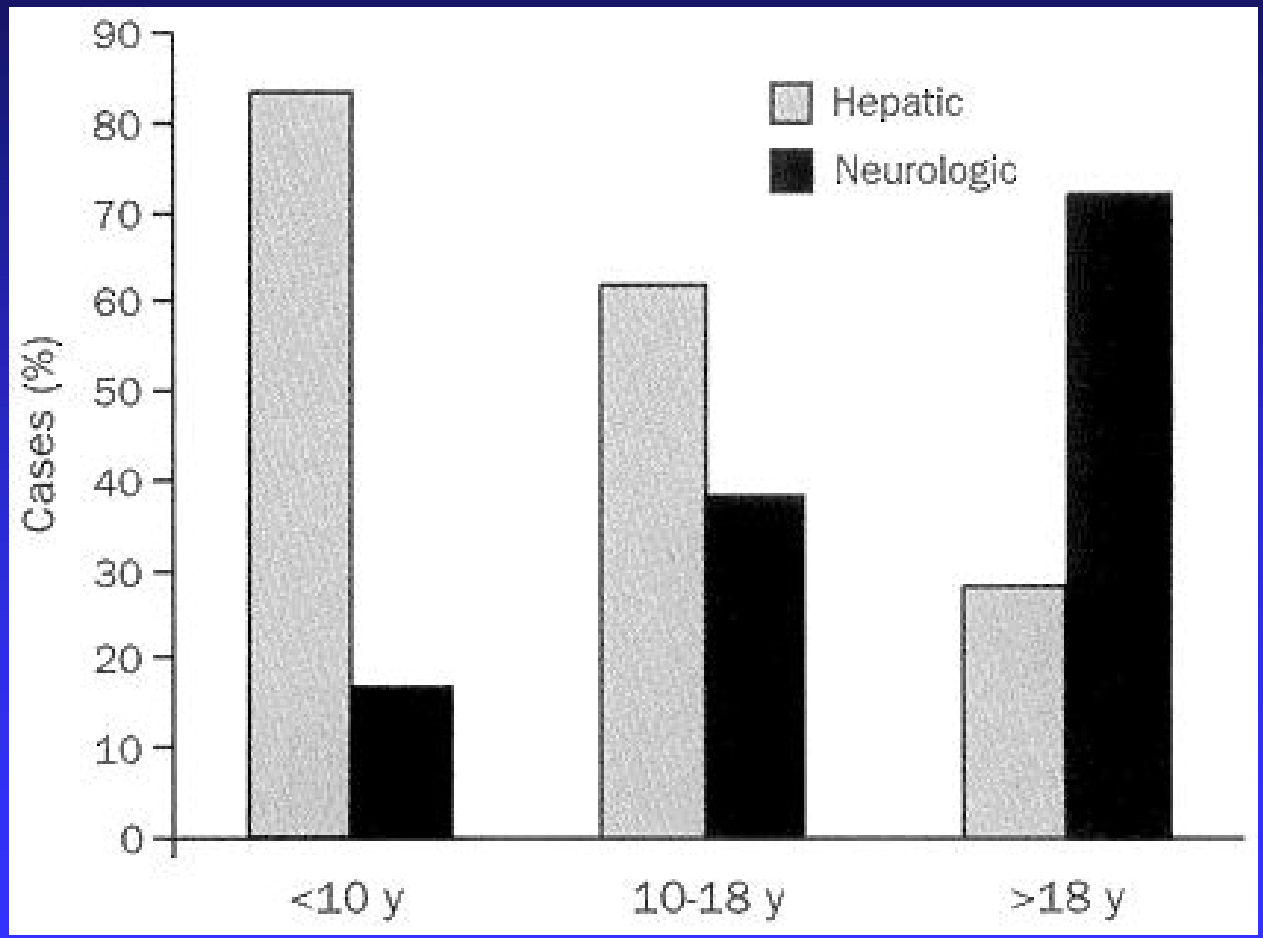
Clinical Presentation

- Majority of clinical cases present between the ages of 5 and 35
- Youngest case in the literature was a 3 year old patient
- Oldest patients described were 2 siblings in their seventies
- Variability in age probably reflects differences in mutations and penetrance as well as extragenic factors.

Clinical Presentation

- There are two principle presentations of Wilson Disease
  - Hepatic Disease
  - Neuropsychiatric Disease
- Patients can also present with features of both diseases

Clinical Presentation



Mayo Clin Proc. 2003 Sept;78(9):1126-36

Clinical Presentation - Hepatic

- Asymptomatic liver function test abnormalities (AST > ALT)
- Chronic hepatitis – mild or severe nonspecific symptoms, such as fatiguability, lethargy, malaise, anorexia, nausea, abdominal pain, and itching
- Acute hepatitis – self-limited clinical illness resembling acute hepatitis

Clinical Presentation - Hepatic

- Portal Hypertension – splenomegaly, thrombocytopenia, and leukopenia occasionally predominate
- Fulminant Hepatic Failure – massive hepatocellular necrosis resulting in a large release of copper ions into the circulation, associated with hemolytic anemia, hemoglobinuria, dark urine, and renal failure

Clinical Presentation - Hepatic

- Fulminant Hepatic Failure
  - Coombs-negative hemolytic anemia
  - Coagulopathy unresponsive to parenteral vitamin K administration
  - Rapid progression to renal failure
  - Relatively modest rises in serum aminotransferases (typically <2000)
  - Normal or markedly subnormal serum alkaline phosphatase (typically <40)
  - Ratio of Alk. Phos. to Total Bil. of <2
  - Female to male ratio 2:1

Clinical Presentation – Hepatic "Mimic" Liver Diseases

- **Autoimmune hepatitis**: acute or chronic presentation similar to AIH, fatigue, malaise, arthropathy, rashes, greatly increased serum immunoglobulin, positive autoantibodies like ANA and ASMA

- **NASH**: severe hepatic steatosis

AASLD Practice Guideline

- Patients in the pediatric age bracket who present a clinical picture of autoimmune hepatitis should be investigated for WD.
- Adult patients with atypical autoimmune hepatitis or who respond poorly to standard corticosteroid therapy should also be investigated for WD
- WD should be considered in the differential diagnosis of patients presenting with nonalcoholic fatty liver or who have pathologic findings of NASH

Clinical Presentation - Neuropsychiatric

- Neuropsychiatric disorders are present in up to 35% of patients with Wilson's disease.
- All of them usually have liver disease which may be well compensated
- Neurologic - tremor, rigidity, clumsiness of gait, slurring of speech, inappropriate and uncontrollable grinning (risus sardonicus), and drooling
- 10% present with psychiatric problems
- Psychiatric - subtle personality changes, deteriorating performance at school, depression, paranoia, and catatonia

Clinical Presentation - Neuropsychiatric

- Bradykinesia, rigidity, cognitive impairment, and an organic mood syndrome are associated with dilatation of the third ventricle by MRI
- Ataxia and tremor were associated with focal thalamic lesions
- Dyskinesia, dysarthria, and an organic personality syndrome were associated with focal lesions in the putamen and pallidum

Clinical Presentation - Other

- Renal
  - Fanconi syndrome - glucosuria, aminoaciduria, hypouricemia, and proximal renal tubular acidosis
  - Nephrolithiasis secondary to distal renal tubular acidosis
- Rheumatologic
  - Arthropathy with features of premature arthritis
  - Chondrocalcinosis – most commonly in the knee
  - Vitamin D-resistant rickets due renal dysfunction

Clinical Presentation - Other

- Hematologic
  - Recurrent low-grade hemolysis leading to transient episodes of jaundice
- Cardiac
  - Cardiomyopathy
  - Congestive heart failure
  - Conduction abnormalities
- Endocrine
  - Hypoparathyroidism
  - Amenorrhea
  - Testicular atrophy
- Muscle
  - Rhabdomyolysis

Diagnosis

- Age
- Kayser-Fleischer Ring / sunflower cataracts
- Serum aminotransferases
- Ceruloplasmin
- Serum copper
- Serum nonceruloplasmin copper
- Urinary copper excretion
- Liver biopsy
- Hepatic parenchymal copper concentration

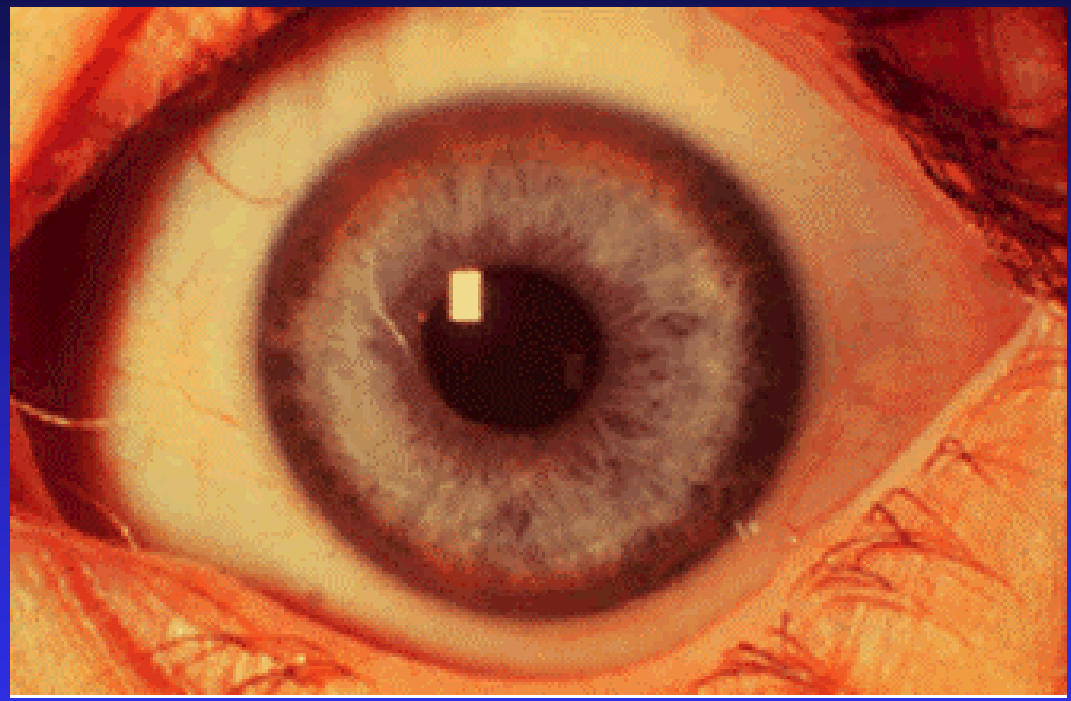
Age

- AASLD Practice Guideline:
  - Wilson Disease should be considered in any individual between the ages of 3 and 45 years with liver abnormalities of uncertain etiology

Serum Aminotransferases

- Usually mildly to moderately elevated
- AST concentration is usually higher than the ALT
- Degree of elevation correlates poorly with the extent of histologic injury

Kayser-Fleischer Ring



- Fine pigmented granular deposits of copper in Descemet's membrane of the cornea
- Most pronounced at the inferior and superior poles of the cornea

Ocular signs

- Kayser-Fleischer Ring
  - In 50-60% of patients with isolated hepatic involvement
  - In 95% of patients with neurologic involvement
  - Not absolutely specific for Wilson's disease
  - Rarely reported in other chronic cholestatic diseases (e.g. PBC, PSC, neonatal cholestasis)
  - Disappear with effective medical treatment
- Sunflower Cataracts
  - Represent copper deposits in the lens

Serum Ceruloplasmin

- 132-kd protein synthesized by hepatocytes and secreted into the circulation
- Accounts for 90% of circulating copper
- Possesses Feroxidase activity and is required for normal transport of iron
- Hence patients with aceruloplasminemia exhibit hemosiderosis

Serum Ceruloplasmin

- Most patients with Wilson's disease have low serum ceruloplasmin levels
- A serum ceruloplasmin concentration less than 20 mg/dL in a patient who also has Kayser-Fleischer rings is considered to be diagnostic of WD
- Acute phase reactant – hence maybe falsely raised into the normal range in Wilson Disease presenting with acute illness

Serum Ceruloplasmin – Low Positive Predictive Value

- Prospective trial with 2867 patients undergoing evaluation of liver disease
- 17 had low serum ceruloplasmin (< 20 mg/dL)
  - Wilson disease - 1
  - Heterozygous carriers - 3
  - Acute Viral Hepatitis – 3
  - Drug-induced Liver Disease – 3
  - Malabsorption - 3
  - Alcohol-induced Liver Disease – 2
  - Chronic Hepatitis – 2

Differential Diagnosis of Low Ceruloplasmin

- Wilson Disease
- Asymptomatic heterozygote carriers (10-20%)
- Renal protein loss (nephrotic syndrome)
- Protein-losing enteropathy
- Severe end-stage liver disease of any cause
- Menke's disease (disorder of copper transport)
- Aceruloplasminemia
- Nutrition copper deficiency (eg. inadequate copper in TPN)

AASLD Practice Guideline

Serum ceruloplasmin should be routinely measured during the evaluation of unexplained hepatic, neurologic or psychiatric abnormalities in children and adults through middle age. An extremely low serum ceruloplasmin (<5mg/dL) should be taken as strong evidence for the diagnosis of WD

Serum Copper

- Serum copper is decreased in proportion to the reduction in serum ceruloplasmin
- Serum nonceruloplasmin-bound copper levels are raised – greater than 25 mcg/dL in the majority of untreated patients (normal <15 mcg/dL)
- Marked elevation may be seen in fulminant hepatic failure due to Wilson's disease, where copper is released suddenly from tissue stores.

Serum Nonceruloplasmin Copper or Serum Free Copper

- Sensitivity, specificity, and predictive values of the nonceruloplasmin-bound copper concentration as a diagnostic test for Wilson's disease have not been well-established
- May be elevated in acute liver failure of any etiology and in patients with chronic cholestasis
- Decreased values have been reported in patients overusing zinc supplements

Urinary Copper Excretion

- Wilson Disease is typically associated with 24-hour urinary copper excretion of >100 mcg
- Lower values have been described in up to 25 percent of presymptomatic patients with confirmed Wilson Disease
- Normal values are in the range of 30 to 40 mcg/day
- A value >40 mcg/day warrants further investigation (AASLD Practice Guideline)

Hepatic Parenchymal Copper Concentration

- Quantitative hepatic copper concentration >250 mcg of copper per gram of dry weight (normal <50 mcg/gm of dry weight) is generally considered to be the gold standard for diagnosis of WD
- False negatives are possible
  - Uneven copper distribution within a cirrhotic liver
  - Massive release of copper from necrotic hepatocytes as in fulminant hepatic failure
- False positive are possible in patients with chronic cholestasis

Hepatic Parenchymal Copper Concentration

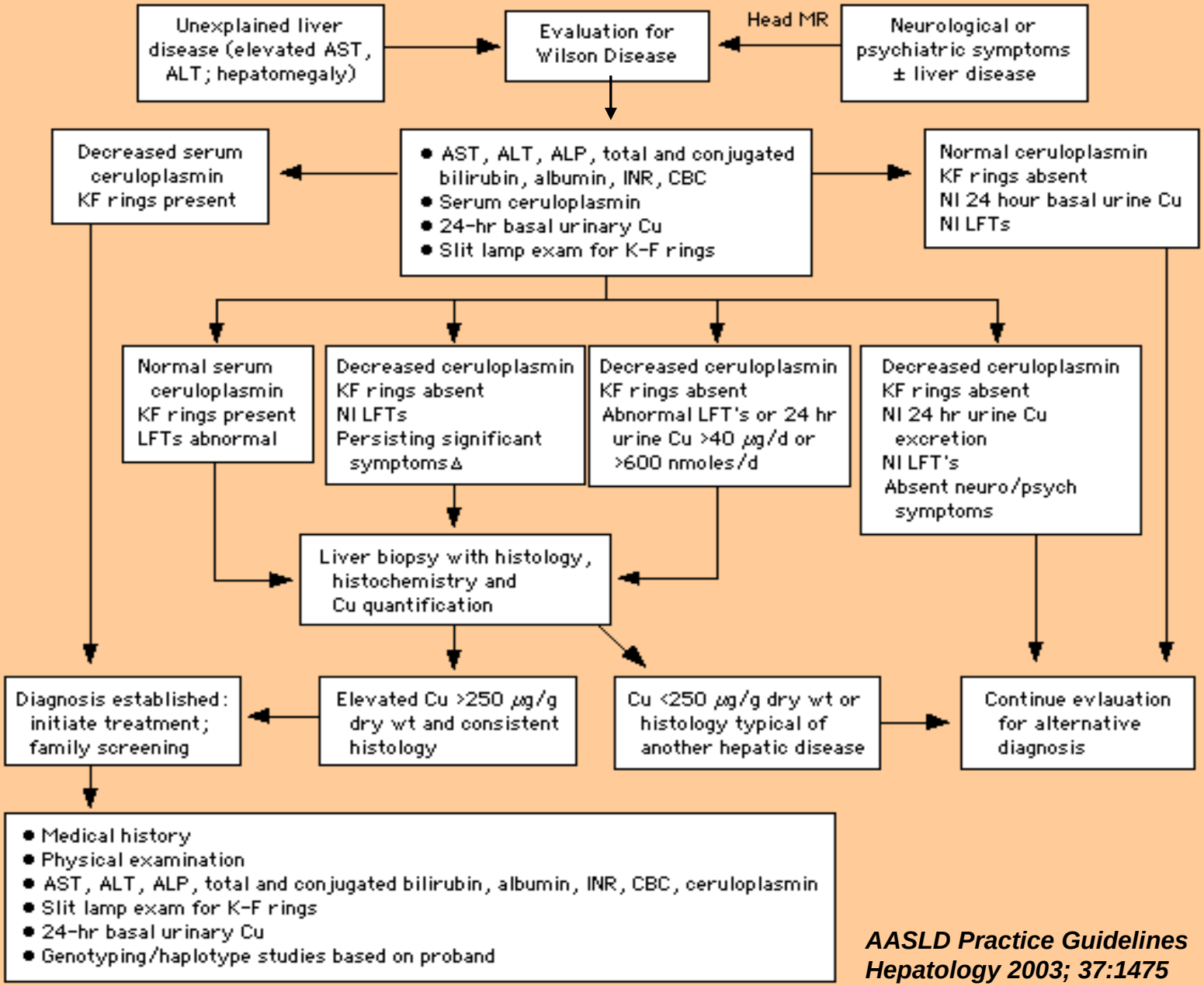
- AASLD Practice Guideline
  - Hepatic parenchymal copper content greater than 250 mcg/gm dry weight provides critical diagnostic information and should be obtained in cases where the diagnosis is not straightforward and in younger patients.
  - In untreated patients, normal hepatic copper content (<40-50) excludes a diagnosis of WD

Genetic Studies

- Abundance of disease-specific mutations and their location at multiple sites across the genome have limited the utility of molecular diagnosis
- Most patients are compound heterozygotes
- Direct mutation analysis or haplotype analysis can be used to test first degree relative of a confirmed patient to determine whether they are unaffected, heterozygous or patients of WD

Neurologic Evaluation

- AASLD Practice Guideline:
  - Neurologic evaluation and radiologic imaging of the brain, preferably by MR, should be considered prior to treatment in all patients with neurologic WD and should be part of the evaluation of any patient presenting with neurologic symptoms consistent with WD



AASLD Practice Guidelines
Hepatology 2003; 37:1475

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

Treatment

- Chelating agents – D-Penicillamine, Trientine, Tetrathiomolybdate
- Zinc
- Liver Transplantation
- Diet
- Antioxidants

D-Penicillamine

- Chelates copper and causes cupriuresis
- 10-50% of patients treated could have worsening of neurologic symptoms
- Severe side-effects requiring discontinuation occur in 20-30% of patients
- SE – cutaneous eruptions, lymphadenopathy, neutropenia, thrombocytopenia, aplasia, proteinuria, nephrotoxicity, lupus-like syndrome, Goodpasture syndrome, serous retinitis, hepatotoxicity and hepatic siderosis from over suppression of copper

Trientene

- Chelates copper and causes cupriuresis
- Indicated in patients who are intolerent of penicillamine as well as a first line agent
- Better tolerated than D-penicillamine
- SE – gastritis, aplastic anemia/pancytopenia (rare), sideroblastic anemia from over suppression of copper, forms a toxic complex with iron and hence coadministration with iron should be avoided

Zinc

- Induces enterocyte metallothionein
- Metallothionein has greater affinity for copper than for zinc, thus preferentially binds to copper in the enterocyte and inhibits its entry into the portal circulation
- May also act by inducing hepatocellular metallothionein
- Well tolerated
- SE – gastric irritation, biochemical pancreatitis

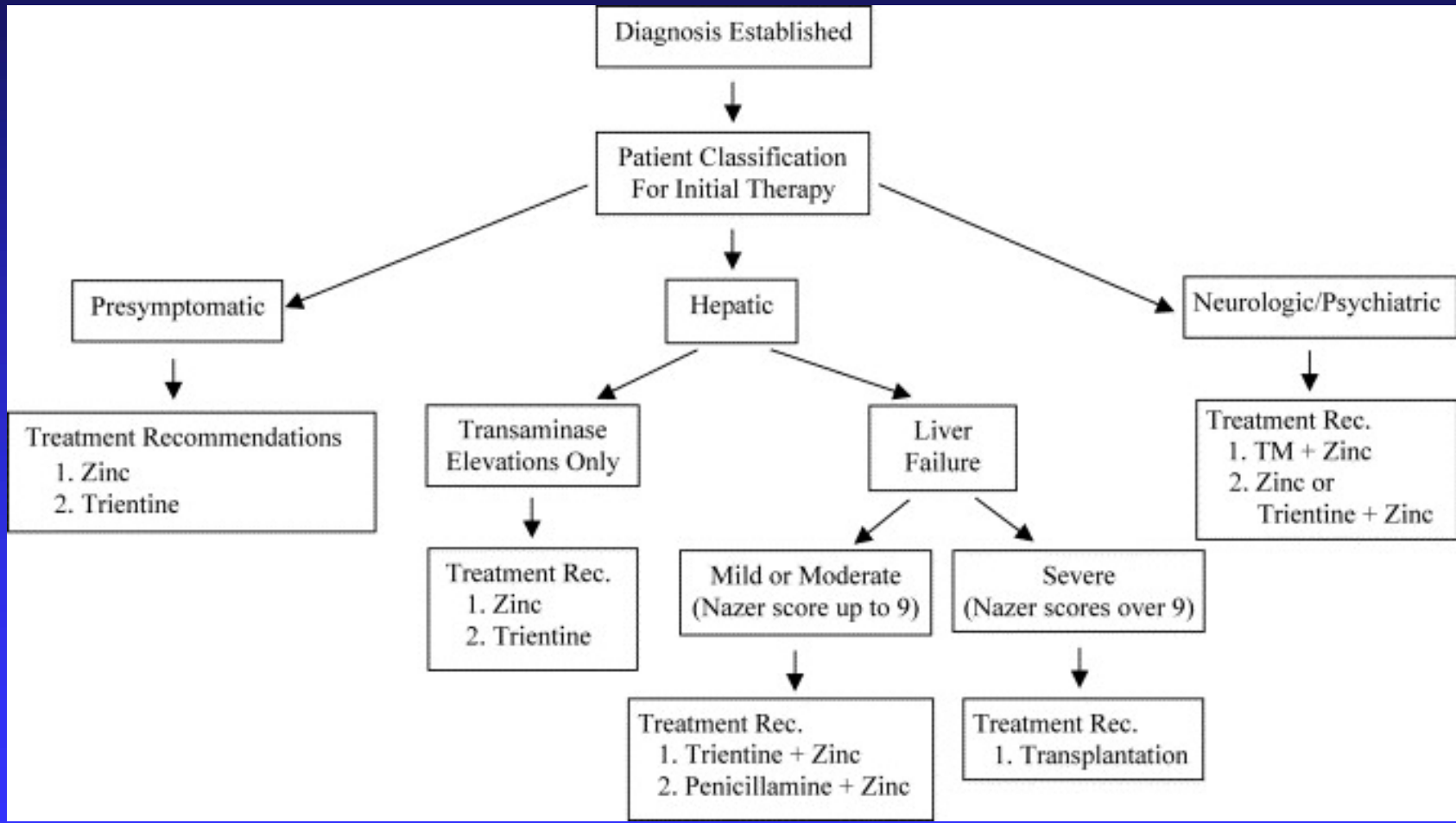
Tetrathiomolybdate

- Chelating agent
- Does not worsen neurologic symptoms like D-penicillamine and Trientene to a lesser extent
- Useful in neurologic disease
- Has been in clinical trials
- Not yet commercially available

Diet

- Avoid foods containing high concentration of copper – shellfish, nuts, choclate, mushrooms and organ meats – at least in the first year of medical therapy
- Evaluate copper content in domestic water supply if being piped through copper pipes or coming from a well

Treatment



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

Classification of hepatic failure based upon the prognostic index of Nazer et al.

Laboratory measurement	Normal value	Score (in points)				
		0	1	2	3	4
Serum bilirubin	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 in seconds (PT)	–	<4	4–8	9–12	13–20	>20

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

AASLD Practice Guidelines

- Initial treatment for symptomatic patients should include a chelating agent
- Treatment of presymptomatic patients or maintenance therapy of successfully treated symptomatic patients can be accomplished with the chelating agent or with zinc
- Treatment should not be discontinued unless a liver transplant has been performed
- Treatment should be continued during pregnancy (dose reduction advisable for D-penicillamine and trientene)

Cancer risk in Wilson Disease

- Whether patients with Wilson's disease are at increased risk for hepatocellular carcinoma or other malignancies is unclear
- Occasional reports have described hepatocellular carcinoma and cholangiocarcinoma
- Screening for hepatocellular carcinoma has not been recommended in the AASLD Practice Guidelines

Case Presentation

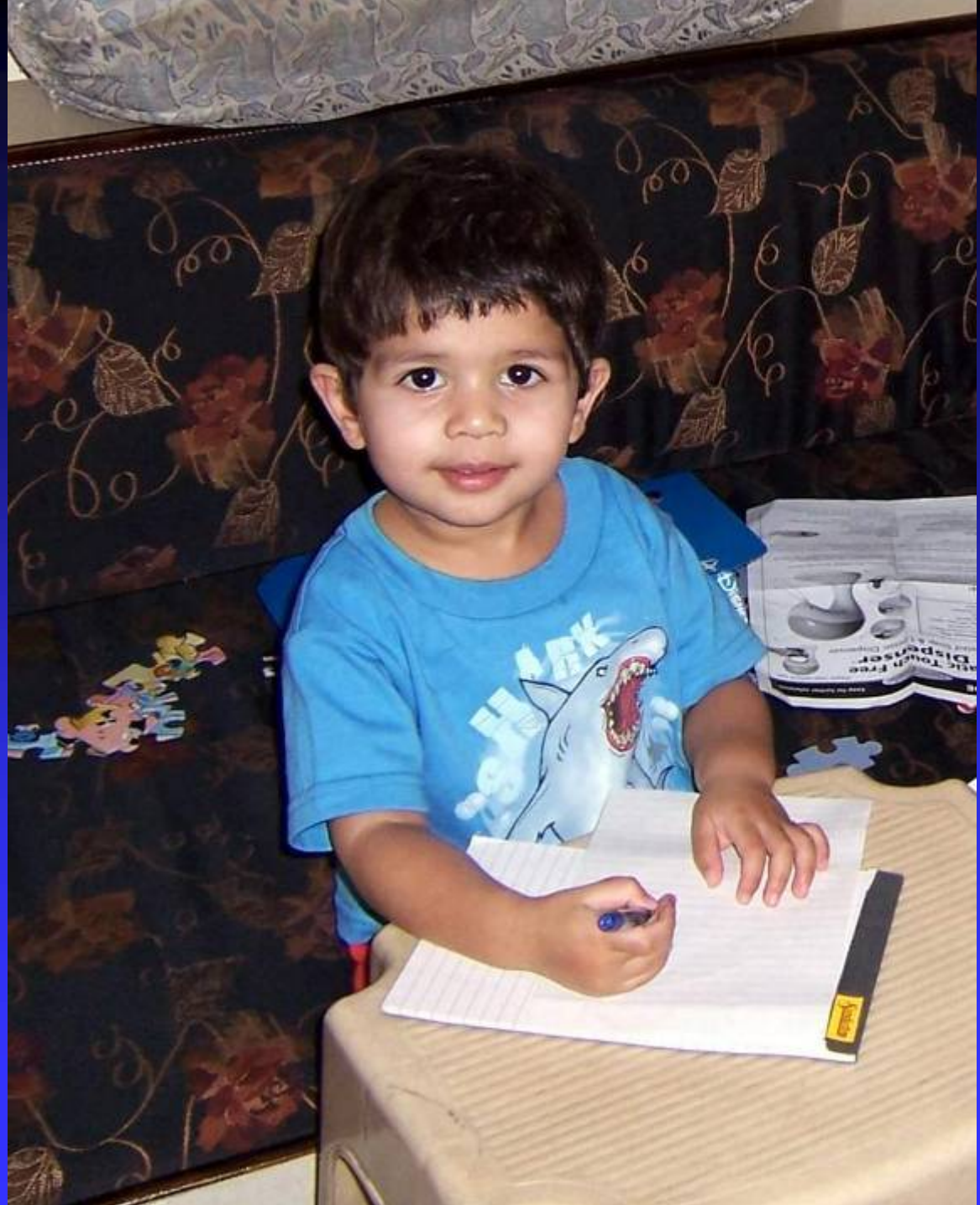
- Our patient was treated initially with D-penicillamine and is maintained on trientine at present
- She initially presented in 1988 and her disease has been successfully controlled with medical therapy to date
- Her cirrhosis resolved

Case Presentation

- Latest Liver Biopsy report:
  - Moderate steatosis with slight distortion of the hepatic architecture and mild periportal chronic inflammation
  - Stage 1 Fibrosis

Take Home Points

- WD should be considered in any individual between the ages of 3 and 45 with liver function abnormalities
- WD should be suspected in any patient with fulminent liver failure associated with Coombs negative hemolytic anemia, unresponsive coagulopathy, renal failure and modest AST/ALT elevations – liver transplantation can be lifesaving
- Medical treatment of WD is lifelong – and withdrawal of treatment could result in rapid deterioration of liver function requiring transplant



Acknowledgements

- Dr Richard Wright
- Dr Luis Marsano
- Steve Mahanes