

Wilson Disease - Our Experience



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Key Concepts

- Wilson disease is more often considered than found, but if not considered will not be found.
- Prevalence 1:30.000
- Rarely before 3-4 y old. Usually appears II -IV decade
- WD should be considered in the D.D. of any unexplained liver disease, especially in these with liver disease & neurological or psychiatric symptoms.



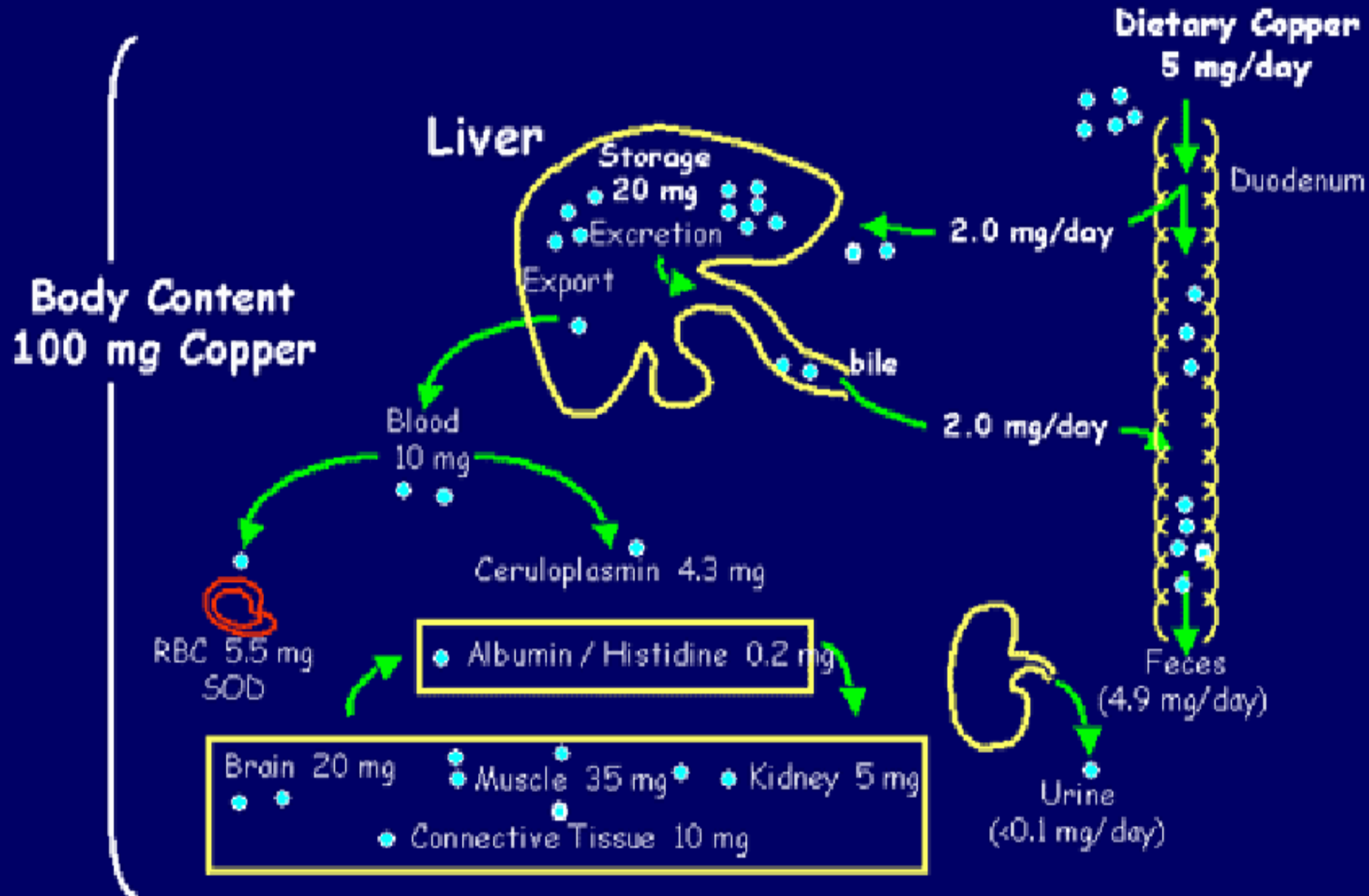


Key Concepts

- Autosomal recessive - gene localized to chromosome 13q14.3-q21.1.
- Gene encodes a p-type ATP-ase **ATP7B**.
- It is responsible for copper excretion in bile and copper incorporation in ceruloplasmin
- ↓ biliary copper excretion
- ↑ Hepatic copper accumulation
- → Copper deposition in extra hepatic sites
- Pathophysiology related to copper over load



Human Copper Metabolism





Ceruloplasmin

- 132 kd protein, synthesized in liver.
- Acute phase reactant, copper carrying protein.

Increased

Inflammation

Neonatal period

Hepereestrogenemia

Pregnancy

Oral contraceptive

Decreased

Aceruloplasminemia

Renal disease

Enteric loss

End stage liver disease

Copper deficiency

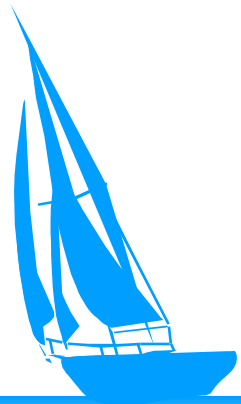
Early infancy





Indications for Testing

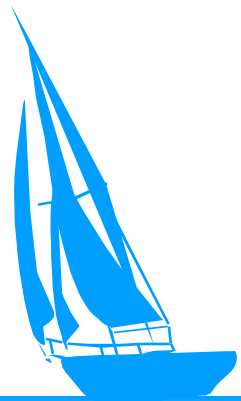
- Unexplained abnormal liver enzymes
- Unexplained hemolysis
- Neurological disturbances
- Fanconi's syndrome
- Hypouricemia
- Keiser- Fleisher ring
- Siblings of affected patients





Clinical Features

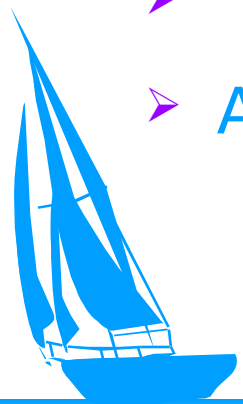
- Hepatic (50%)
- Neurologic (40-50%)
- Psychiatric (10-25%)
- Hemolytic anemia (15%)
- Renal – Fanconi’s syndrome
(rare)





Hepatic Manifestations

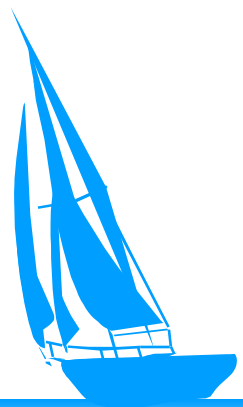
- Hepatomegaly
- Elevated liver enzymes
- “Recurrent” hepatitis
- Chronic Active hepatitis
- Cirrhosis
- portal hypertension
- Acute liver failure, fulminant hepatitis





Neurologic Manifestations

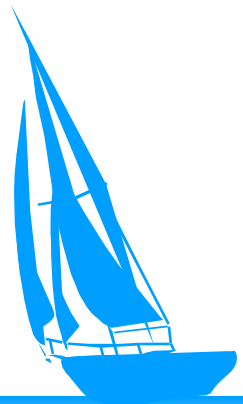
- Movement disorders: tremor & chorea
- Dystonia
- Pseudobulbar palsy
- Seizures
- Hypokinesia
- Drooling
- Dysarthria





Psychiatric Manifestations

- Personality disturbances
- Depression
- Neurosis
- Psychosis





Other Systems

- **Blood**- hemolytic anemia
- **Renal** – aminoaciduria, nephrolithiasis
- **Skeletal** – osteoporosis, arthritis
- **Cardiac** – cardiomyopathy, dysrhythmias
- **GYN** – infertility, amenorrhea, repeated miscarriages

Pancreatitis

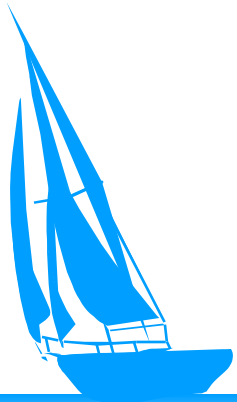
Hypoparathyroidism





Wilson Disease

Diagnosis

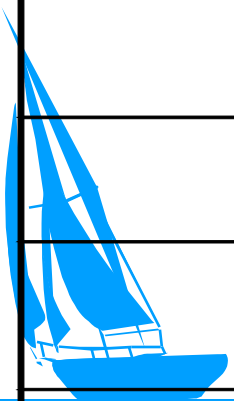


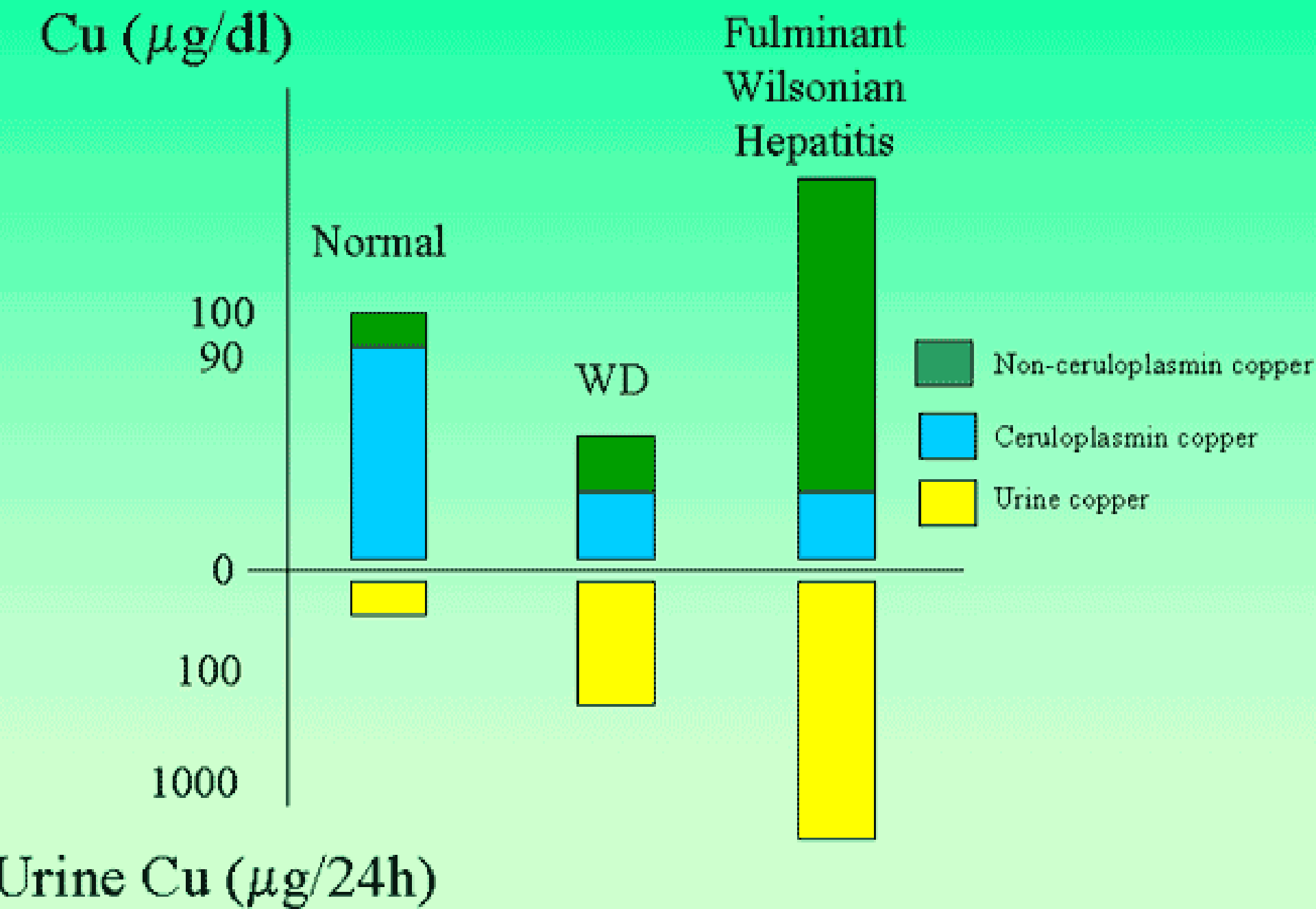
Diagnosis of Wilson Disease

	Normal	Wilson's
• Serum Copper (micgm/dl)	80-140	<80
• Urine Copper (mcg/24 hr)	<40	>100
• Serum ceruloplasmin (mg/dl)	20-40	<20
• Hepatic copper (micg/gm dw)	15-50	250-3000
• Serum Free-Copper Concentration = Total Cu - Ceruloplasmin X 3.15		
– Free Cu usually < 100 $\mu\text{g/L}$		
– Wilson's Disease: Free Cu >200 $\mu\text{g/L}$		



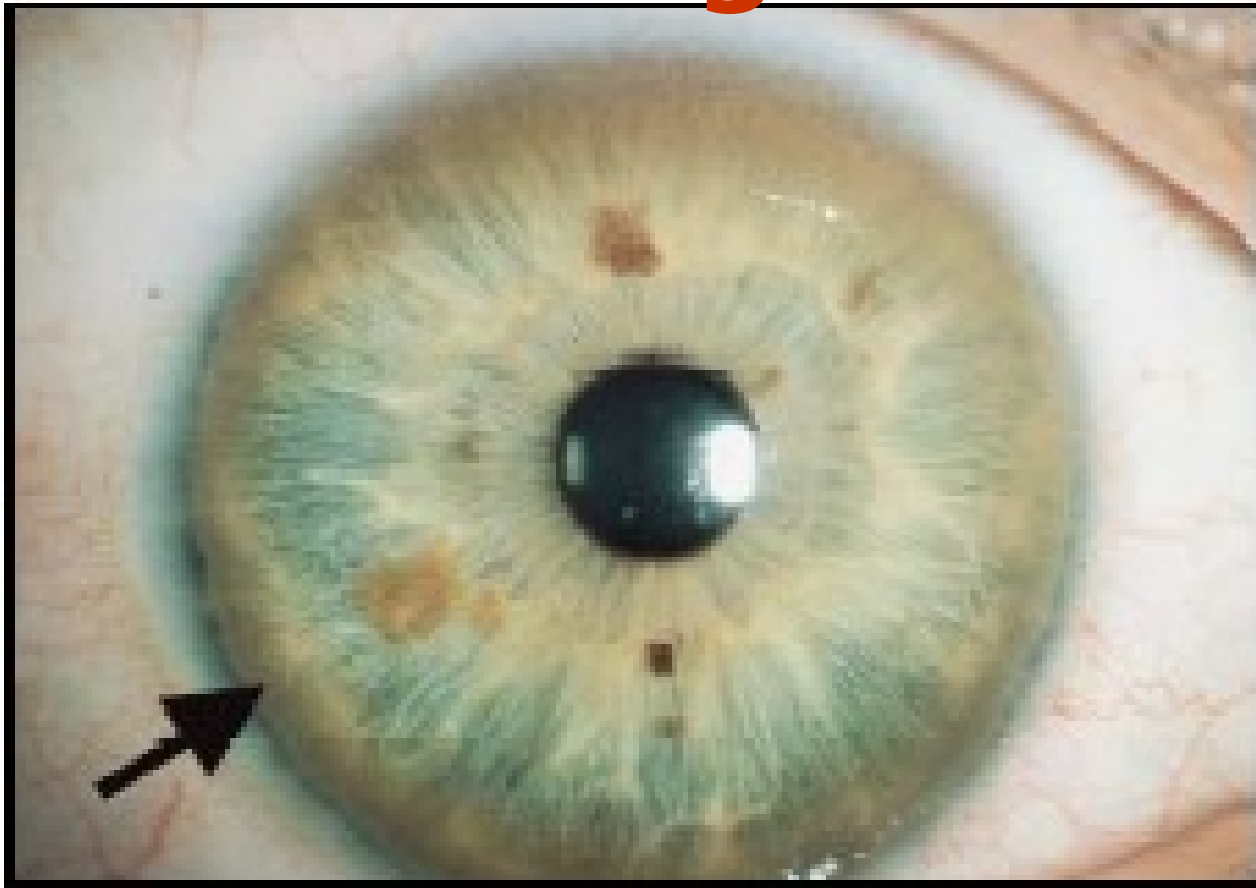
Mean Hepatic Cu (mcg/gr dry weight)	Disease
730	Wilson's Disease
410	Primary Biliary Cirrhosis
245	Primary Sclerosing Cholangitis
130	Extra hepatic Biliary Obstruction
1830	Indian Childhood Cirrhosis
40	Alcoholic /Cryptogenic Cirrhosis
30	Normal





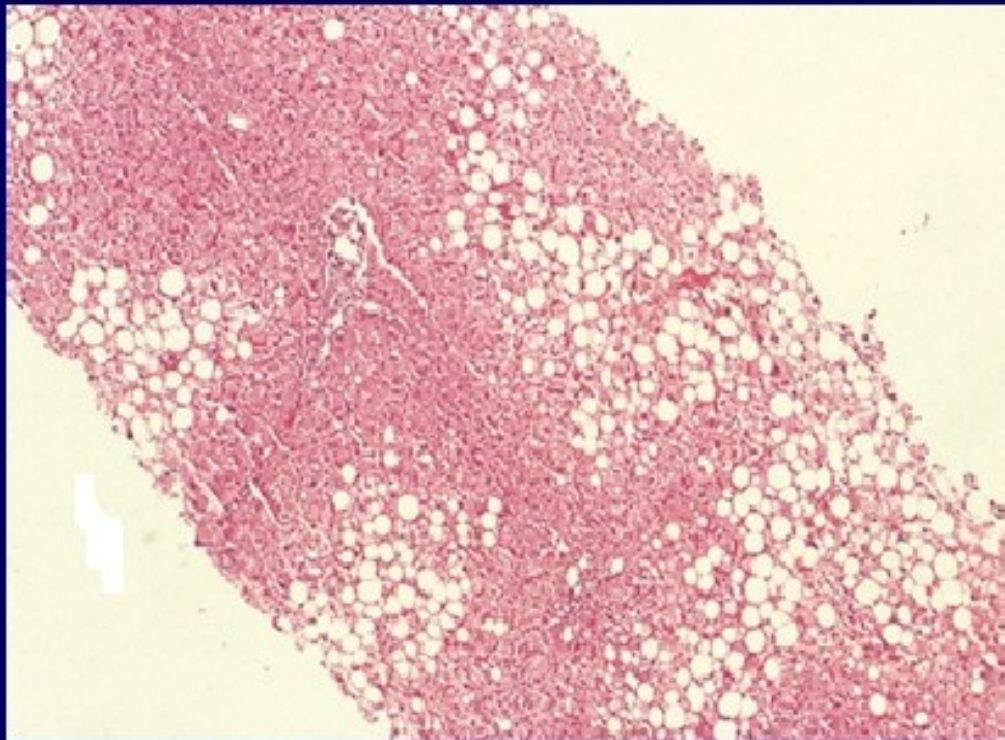


Kayser-Fleischer Ring



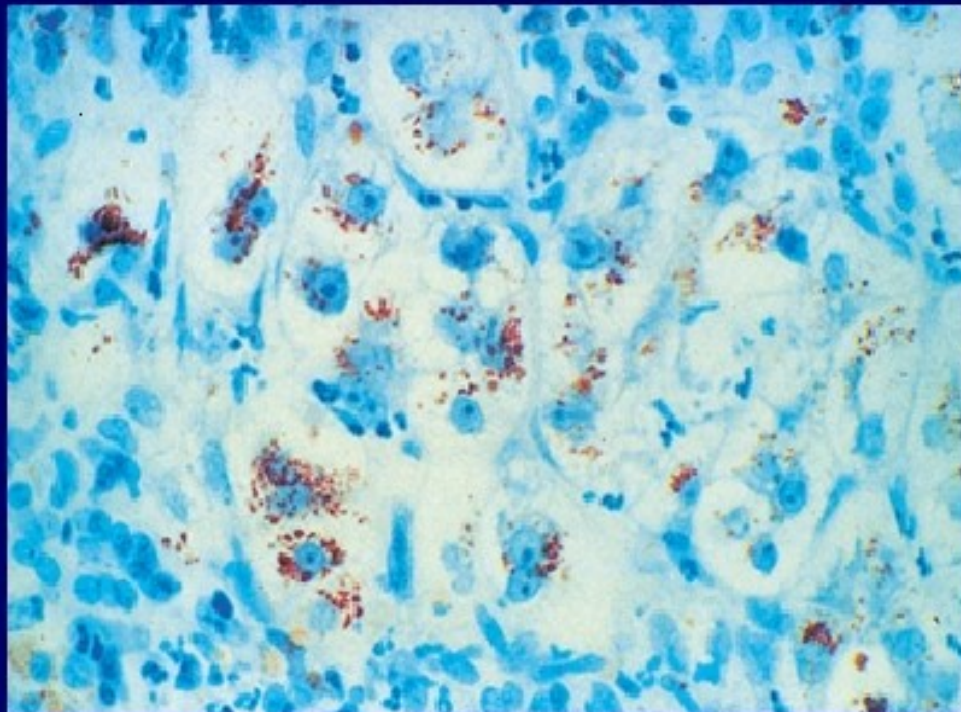


Wilson Disease



Macro and
microvesicular
steatosis

Wilson Disease



Copper stain
(rhodanine)

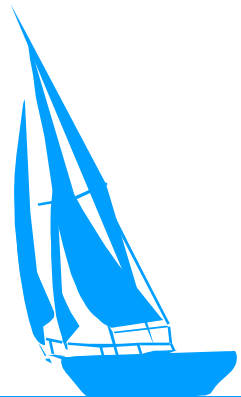
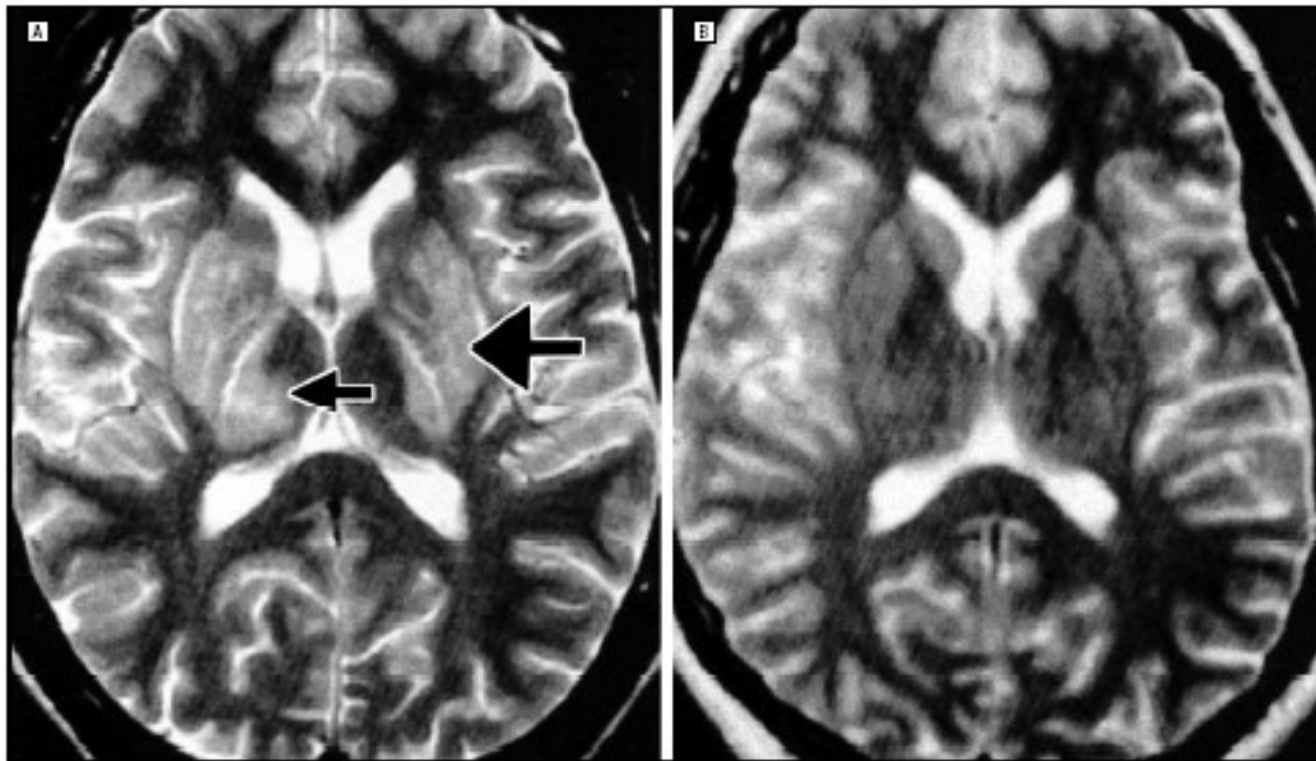


MRI

Deposition of Copper in the Basal Ganglia

Wilson

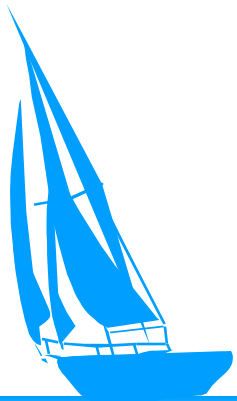
Normal





Genetic Test

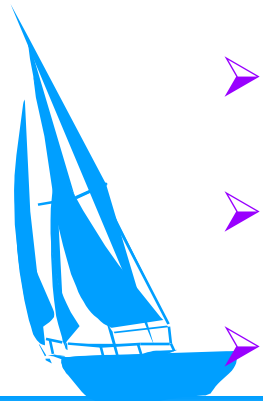
- Large gene & protein
- >200 mutation
- Compound heterozygote
- Homozygote





Treatment

- Lifelong treatment
- Asymptomatic & active disease
- Diet
- D-Penicillamine
- Trientine
- Zinc
- Ammonium tetrathiomolybdate
- Liver Transplantation





Diet: Eliminate Copper

Rich Diet

- Organ meats
- Shellfish
- Nuts
- Chocolate
- Mushrooms
- Dried fruits or beans
- Water supply





D-Penicillamine

- General chelator
- Induce cupriuria
- Induce metallothionein
- Well absorbed, meal decrease absorption
- **Monitoring**: urinary copper 250-500ug
- Normalization of nonceruloplasmin-copper





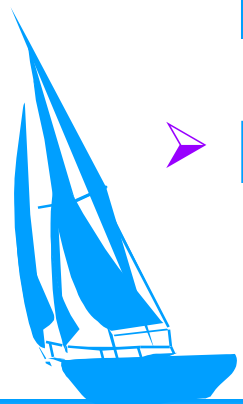
D-Penicillamine Side Effects

- **Neurologic deterioration at initial treatment - common**
 - **Hypersensitivity reaction:** fever, rash, lupus like
 - **Bone marrow suppression:** aplastic anemia, leukopenia, thrombocytopenia
 - **Renal:** Nephritis, nephrosis
 - **Dermatologic:** interferes with collagen synthesis - Degenerative changes, wound healing
 - **Hepatotoxicity**
- 



Trientine

- General chelator; induces cupriuria
- Better safety profile than penicillamine
- Ideal drug to Pt with penicillamine intolerance
- Poorly absorbed





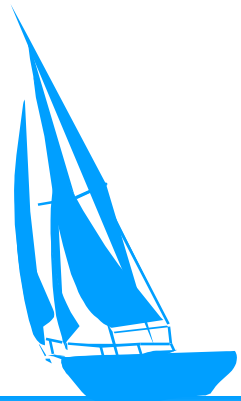
Trientine

Side effects:

- Neurologic deterioration at initial treatment - rare
- Gastritis

Rare side effects

- Aplastic anemia
- Sideroblastic anemia





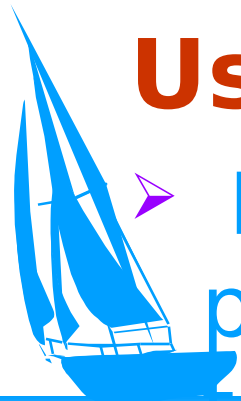
Zinc

Mode of action:

- Mettallothionenin inducers
- Blocks intestinal absorption of copper

Usage:

- For asymptomatic, maintenance pregnancy and in combination therapy





Zinc

No neurologic deterioration

Poorly absorbed with food

Side effects:

- Gastric irritation, Gastritis
- Pancreatitis – biochemical
- Zinc accumulation
- Possible change in immunologic function
- **Monitoring:** urinary copper < 75ug, normalization of nonceruloplasmin- copper



Tetrathiomolybdate

e

Mode of action:

- General chelator
- Blocks intestinal absorption of copper
- Induces intestinal and urinary copper loss

Side effects:

- Anemia
- Neutropenia





Fulminant Hepatic Failure

May cause fatigue, hepatic insufficiency, extreme jaundice (because of accompanying hemolysis), severe coagulopathy, ascites, hepatic coma, renal failure and death if liver transplantation is not performed

Interventions to reduce secondary organ injury while awaiting a suitable donor organ: albumin dialysis, plasmapheresis, exchange transfusion



Liver transplant remains the treatment of choice for fulminant hepatic failure



Our Patients

- 7 children with elevated liver enzymes which were found in routine blood testing
- 3 of them were diagnosed as WD
- No patient was found with hepatic, neurological, psychiatric or hemolytic manifestations

Clinical examination – normal





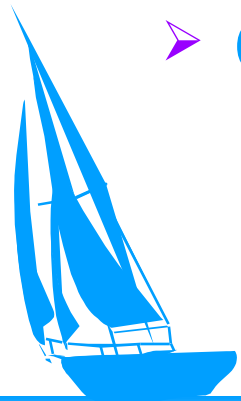
Laboratory Tests

Viral:

- HBsAg
- HCV Ab
- HAV Ab
- EBV IgM
- CMV IgM

Immunologic:

- Immunoglobulins
- Antiparietal cell Ab
- Anti mitochondrion Ab
- Anti smooth muscle Ab
- ANA
- LKM
- Anti endomesial Ab
- AFP



Abed	
5	Age (years)
M	Gender
-	Relatives with Wilson
95	AST (u/l)
125	ALT (u/l)
Fatty liver	US
18	Ceruloplasmin(mg/dl)
95	Cu in serum (mcg/l)
171	Cu in urine (24h) (mcg/l)
575	Cu after penicillamin (mcg/l)
-	Keiser-Fleisher ring
+	Liver histology: Steatosis
-	Orcein
-	Rhodenin
-	Cirrhosis
940	Cu in liver(mcg/gr dry weight))

Moad
10
M
+
159
90
N
22
85
330
4800
-
+
-
-
-
1520

Nur
6
F
-
170
125
Fatty liver
9
26
106
477
-
+
+
-
+
1480
Homoz



Coay	Hadil	Adham	Ali	Nur	Moad	Abed	
13	9.5	12.11	8	6	10	5	Age(year)
M	F	M	M	F	M	M	Gender
-	-	+	-	-	+	-	Relatives with Wilson
43	66	28	63	170	159	95	AST(u/l)
52	95	31	73	125	90	125	ALT(u/l)
Fatty liver	N	Fatty liver	Fatty liver	Fatty liver	N	Fatty liver	US
2.5	25	23.6	32	9	22	18	Ceruloplasmin(mg/dl)
148	129	110		26	85	95	Cu in serum(mcg/dl)
45	168	140		106	330	171	Cu in urine (24h)(mcg/dl)
645	760	456	904	477	4800	575	Cu after penicillineam (mcg/dl)
-	-	-	-	-	-	-	Keiser-Fleisher ring
+	-	+		+	+	+	Liver histology: Steatosis
-	-	-		+	-	-	Orcein
-	-	-		-	-	-	Rhodenin
-	-	-		+	-	-	Cirrhosis



Conclusions

- All were asymptomatic
- All were found within normal examination
- All without Keiser- Fleischer ring
- US of Abdomen was not informative, liver mostly fatty
- AST not always $>$ ALT





Conclusions - Cont.

- Ceruloplasmin was low in 2 patients
- Ceruloplasmin $>20\text{mg}\%$ in 1 patients
- Cu in serum low in 1 patient . Normal in others
- Cu in urine in 24 hours collections is indicative
- Cu in urine after penicillamine is indicative

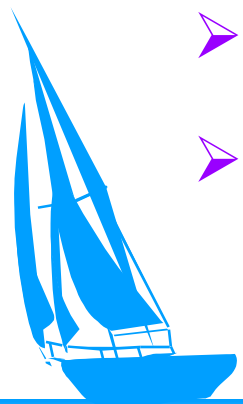




Conclusions - Cont

Liver Histology:

- Most with steatosis
- Orcein stain ***Positive*** in 1 patient
- Rhodanin stain ***Negative***
- Cirrhosis in 1 patient (6 years old)
- Cu level in hepatic tissue is diagnostic





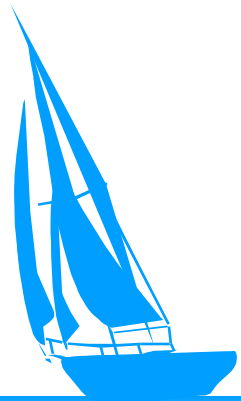
Take Home Message

Consider WD

Do large evaluation

Send to specialist

**Early diagnosis & TRT may
prevent complications and
save lives**





köszönöm ! תודה dĕkuji

mahalo 고맙습니다

thank you

merci 谢谢 *danke*

Ευχαριστώ شڪرا

どうもありがとう *gracias*