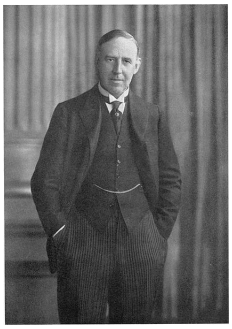
SASL School of Hepatology: 30.09.2013

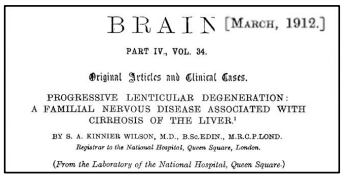
Wilson Disease

David Semela, MD PhD
Fachbereich Gastroenterologie & Hepatologie
Kantonsspital St. Gallen

Kantonsspital St.Gallen

Dr. Samuel Alexander Kinnier Wilson, 1878-1937





BRAIN [MARCH, 1912.]

PART IV., VOL. 34.

Original Articles and Clinical Cases.

PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER.[1]

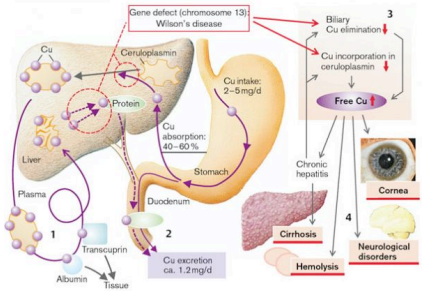
BY S. A. KINNIER WILSON, M.D., B.Sc.EDIN., M.R.C.P.LOND.
Registrar to the National Hospital, Queen Square, London.

(From the Laboratory of the National Hospital, Queen Square.)

2012 – Centenary of the first publication on Wilson's disease

Pathophysiology

Wilson Disease - Pathophysiology

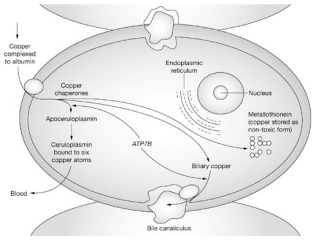


Normal dietary consumption and absorption of copper exceed the metabolic need, homeostasis of copper is maintained exclusively by biliary excretion

Silbernagl/Lang, Color Atlas of Pathophysiology, Thieme 2000

Wilson Disease - Pathophysiology

- Wilson disease is due to mutations of the **ATP7B gene** on **chromosome 13**, which encodes a copper-transporting ATPase (ATP7B)
- The ATP7B gene was identified by three groups in 1993



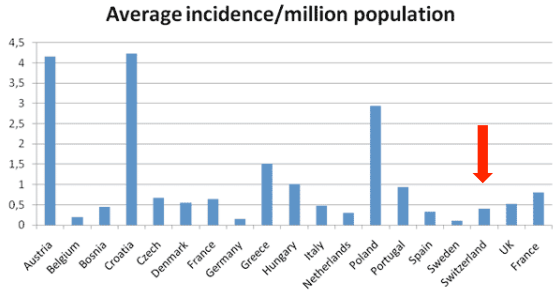
Wilson Disease - Pathophysiology

- Wilson disease is due to mutations of the **ATP7B gene** on **chromosome 13**, which encodes a copper-transporting ATPase (ATP7B)
- ATP7B is responsible for transporting copper from intracellular into the secretory pathway, both for **excretion into bile** and for incorporation into apo-ceruloplasmin for the **synthesis of functional ceruloplasmin**
- The development of Wilson disease is due to the accumulation of copper in affected tissues

Wilson Disease - Pathophysiology

- WD is an **autosomal-recessive** genetic disorder found worldwide
- **Gene frequency** of 1 in 90–150
- **Incidence** as high as 1 in 30,000
- More than **500 distinct mutations** have been described in the Wilson gene, from which 380 have a confirmed role in the pathogenesis of the disease
- Most patients are **compound heterozygotes**, which makes phenotype/genotype correlation problematic

Wilson Disease - Incidence



Incidence is underestimated !

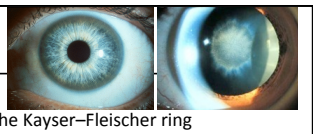
EuroWilson Clinical Database

Clinical Presentation

Wilson Disease – Clinical Presentation

- Clinical presentation can vary widely, but the key features of Wilson disease are:
  - Corneal **Kayser-Fleischer** rings
  - **Liver disease** & cirrhosis
  - **Neuropsychiatric** disturbances (i.e. tremor, ataxia, dystonia)
  - Acute episodes of **hemolysis**
- The most common presentations are with liver disease or neuro-psychiatric disturbances
- WD not just a disease of children and young adults, but may present at **any age** (majority ages 5-35; only 3% >40 years)

Kayser-Fleischer Rings



- The clinical hallmark of WD is the Kayser–Fleischer ring
- Caused by deposition of copper in Desçemet's membrane of cornea
- Present in **95% of patients with neurologic symptoms**
- In **>50%** of those without neurologic symptoms
- In children presenting with liver disease, Kayser–Fleischer rings are usually absent
- A **slit-lamp examination is required** to identify KF rings
- **Not entirely specific** for WD (i.e. in chronic cholestatic diseases such as PBC or in children with neonatal cholestasis)
- Other ophthalmologic changes are rare (i.e. **sunflower cataracts**)

Dr. Bernhard Kayser, 1869-1964 (1902)
Dr. Bruno Otto Fleischer, 1874-1965 (1903)

Dr. Bruno Otto Fleischer

First description of the corneal ring

Klin. Monatsblatt f. Augenheilkunde Vol.41 (1903), p. 489-491.

Clinical Presentation - Liver

- Any type of liver disease my be encountered in WD:
  - Asymptomatic increase in liver tests / **chronic Hepatitis**
  - **Liver cirrhosis** (compensated/decompensated)
  - **Acute liver failure**
- Wilson's disease accounts for **6–12% of all patients with acute liver failure** who are referred for emergency transplantation
- Although cirrhosis is already present in most cases, the clinical presentation is acute and progresses rapidly to hepatic and renal failure and, when untreated, carries an almost **95% mortality**
- An acute presentation with rapid deterioration may also occur in patients who stopped their medications

Clinical symptoms in WD patients presenting with liver disease

Author, Country, [Ref.]	Walshe, UK, [157]	Stremmel *et al.*, Germany, [39]	Schilsky *et al.*, USA, [142]	Scott *et al.*, UK, [158]	Ferenci, Austria, [44]
N with liver disease (out of)	87 (>250)	n.a. (51)	20* (320)	17* (45)	30 (64)
Presenting symptom					
Jaundice, anorexia, vomiting (%)	44	14	15	41	37
Ascites/edema (%)	26	14	50	24	23
Variceal hemorrhage (%)	6		10	6	3
Hemorrhagic diathesis (%)	8				3
Hemolysis (%)	20	10	5		10
Hepatomegaly/splenomegaly (%)	16	49	15	29	17
Acute liver failure (%)	n.a.	n.a.	n.a.	n.a.	17
Asymptomatic§ (%)		18	5		23

* only cases with chronic active hepatitis
§ elevated ALT at routine testing or accidental finding of cirrhosis or of Kayser-Fleischer rings

EASL Clinical Practice Guidelines, 2012

Clinical Presentation - Blood

- **Coombs-negative haemolytic anemia** may be the only initial symptom
- Low-grade hemolysis may be associated with WD even when liver disease is not clinically evident
- Marked hemolysis is commonly associated with severe liver disease
- Decay of liver cells may result in the release of large amounts of stored copper, which further aggravates hemolysis

Clinical Presentation - Neurology

- WD can manifest with **a spectrum of neurological, behavioral or psychiatric disorders**, which may be its first clinical manifestation, appearing simultaneously with hepatic signs, or years later
- Neurological presentation can be **extremely subtle**, and intermitted for many years, but may also develop very rapidly, leading within a few months to **complete disability**
- The neurological abnormalities can be classified as:
  - **Akinetic-rigid syndrome** similar to Parkinson's disease
  - Pseudosclerosis dominated by **tremor**
  - **Ataxia**
  - **Dystonic syndrome**

Clinical Presentation – Psychiatry

- **Behavioral and psychiatric symptoms are common** and some of them may precede neurologic or hepatic signs and symptoms
- **30%** of patients initially present with psychiatric abnormalities
- In children declining **school performance**, **personality changes**, impulsiveness, **labile mood** and inappropriate behavior are observed
- The initial symptoms are frequently misdiagnosed as behavioral problems associated with puberty
- In older persons, psychotic features resembling **paranoia**, **schizophrenia** or **depression** can be observed
- Severe **cognitive deterioration** is observed in patients with advanced neurological disease, but in general, cognitive function is not markedly impaired

Diagnostic Testing

No single test is specific *per se*.

Diagnostic Methods in Wilson Disease

- Serum ceruloplasmin (<0.1g/L)
- Serum „free“ (non ceruloplasmin bound) copper (>200µg/L)
- 24-hour urinary copper excretion (>1.6µmol/24h, >100µg/24h)
- Presence of Kayser-Fleischer rings by slit lamp examination
- Liver biopsy (Histology, Rhodanine stain, Orcein stain, TEM)
- Hepatic parenchymal copper concentration (>4µmol/g dry weight)
- Genetic testing for ATP7B mutations
- MRI of the brain with hyperintense basal ganglia in T2

modified after EASL Clinical Practice Guidelines, 2012

Routine tests for diagnosis of Wilson's Disease

Test	Typical finding	False "negative"	False "positive"
Serum ceruloplasmin	Decreased by 50% of lower normal value	Normal levels in patients with marked hepatic inflammation Overestimation by immunologic assay Pregnancy, estrogen therapy	Low levels in: - malabsorption - aceruloplasminemia - heterozygotes
24-hour urinary copper	>1.6 µmol/24 h >0.64 µmol/24 h in children	Normal: - incorrect collection - children without liver disease	Increased: - hepatocellular necrosis - cholestasis - contamination
Serum "free" copper	>1.6 µmol/L	Normal if ceruloplasmin overestimated by immunologic assay	
Hepatic copper	>4 µmol/g dry weight	Due to regional variation - in patients with active liver disease - in patients with regenerative nodules	Cholestatic syndromes
Kayser-Fleischer rings by slit lamp examination	Present	Absent - in up to 50% of patients with hepatic Wilson's disease - in most asymptomatic siblings	Primary biliary cirrhosis

EASL Clinical Practice Guidelines, 2012

Diagnostic Methods in WD – Ceruloplasmin (1)

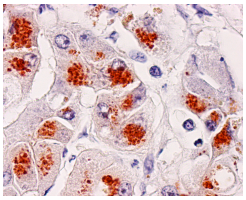
- Ceruloplasmin is the major carrier of copper in the blood and contains six copper atoms per molecule (**holoceruloplasmin**) but may be present just as the protein without the copper (**apoceruloplasmin**)
- Ceruloplasmin is an **acute phase reactant**
- The normal concentration of ceruloplasmin measured by enzymatic assays varies among laboratories (with a **lower limit between 0.15 and 0.2 g/L**)
- In WD ceruloplasmin is usually **<0.1 g/L**
- Serum ceruloplasmin concentrations are **elevated by acute inflammation**, in states associated with hyperestrogenemia such as **pregnancy** and **estrogen supplementation**

Diagnostic Methods in WD – Ceruloplasmin (2)

- Ceruloplasmin is typically decreased in patients with neurologic Wilson disease, but may be in the **low normal range in 50%** of patients with **active Wilson's liver** disease
- Ceruloplasmin may be low in other conditions with **marked renal or enteric protein loss**, **malabsorption** syndromes or with severe **end-stage liver disease** of any etiology
- **20% of heterozygotes** have **decreased levels** of ceruloplasmin
- **Positive predictive value** of subnormal ceruloplasmin in patients with liver disease **only 6%** (Sanchez-Albisua I et al. 1999)

Therefore, serum ceruloplasmin alone is not sufficient to diagnose or to exclude Wilson disease !

Diagnostic Methods in WD: Rhodanine (Orcein) staining

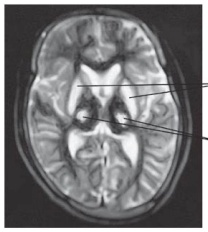


Red-brown cytoplasmic granules coresond to copper deposits in the liver of patients with Wilson's diasease

urmc.rochester.edu

- Focal copper stores on immunohistochemistry **detectable in only <10%** of cases
- Therefore, measurement of **hepatic parenchymal copper concentration** is the **method of choice for diagnosis of WD**
- **Hepatic copper content** of **>250ug/g (4umol/g) dry weight** is confirmative of WD (**sensitivity 83.3%**, **specificity 98.6%**)
- Lower treshhold of **75ug/g (1.2umol/g)**: **96.5% sensitivity**, acceptable **specificity 95.4%**
- Dry weight **<40-50ug/g (0.63-0.8umol/g)** in untreated patients virtually excludes WD

Diagnostic Methods in WD: Neuroimaging



MRI of the brain with hyperintense basal ganglia in T2

Shyamal et al. Nature Clinical Practice Neurology, 2006

- **MRI is the most important diagnostic tool** in patients with neurological presentation
- Almost all patients show an MRI abnormality: **non-specific changes** in the brain such as diffuse brain atrophy and focal abnormalities
- These are shown as **increased signal activity on T2-weight images** in **lenticular, thalamic** and **caudate nuclei** as well as in the **brain stem, cerebellum** and **white matter**.

Wilson Disease Scoring System (Leipzig Score)

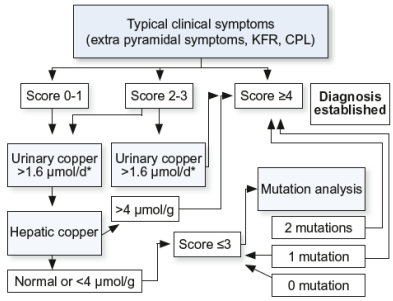
Serum ceruloplasmin:	<0.1g/L = **2**	0.1-0.2g/L = **1**	>0.2g/L = **0**
24-hour urinary copper excretion:	>2x ULN = **2**	1-2x ULN = **1**	Normal = **0**
Presence of Kayser-Fleischer rings:	Present = **2**	Absent = **0**	
Neurologic Symtoms*:	Severe = **2**	Mild = **1**	Absent = **0**
Liver copper(no cholestasis present):**	>4µmol/g = **2**	0.8-4µmol/g = **1**	<0.8µmol/g = **-1**
Genetic testing for ATP7B mutations:	2 chromosomes = **4**	1 chromosome = **1**	
Coombs-negative hemolytic anemia:	Present = **1**	Absent = **0**	

Score Interpretation:		
	≥ 4 points:	diagnosis established
	3 points:	diagnosis possible but more tests needed
	≤ 2 points:	diagnosis very unlikely

*or typical abnormalities at brain MRI
** Rhodanine-positive granules if no quantitative liver copper available

modified after EASL Clinical Practice Guidelines, 2012

Diagnostic algorithms for WD (Leipzig Score)



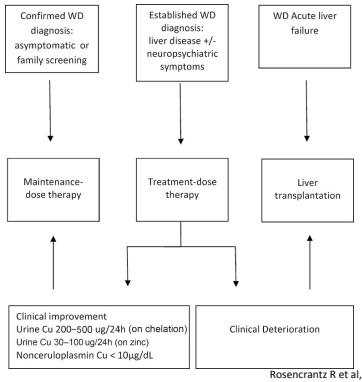
* In children the cut off can be lowered to 0.64 µmol/d

EASL Clinical Practice Guidelines, 2012

Treatment

Untreated Wilson's Disease is fatal.

WD Treatment (1)



Rosencrantz R et al, Semin Liver Dis 2011

WD Treatment (2)

- **Copper chelation** is the most effective treatment
- Available drugs include: **D-penicillamine**, **trientine**, **zinc**, **tetrathiomolybdate**, and **dimercaprol**
- **D-Penicillamine is the treatment of choice** (starting dose 250mg/d increasing to 1500mg/d)
- Once the diagnosis is established, **treatment needs to be life-long**
- There is a lack of high-quality evidence to estimate the relative treatment effects of the available drugs in Wilson's disease
- To date, there is **not a single randomized controlled trial** conducted in Wilson's disease which has an optimal design

WD Treatment (3): Regimens & Follow-Up

Medical Therapy	Treatment/Symptomatic Dose	Side Effects	Monitoring	Maintenance Dose
Penicillamine	Adults: 750–1500 mg divided BID – QID (~20 mg/kg/d to maximum 2 g/d)	Fever	Free Cu 5–15 μg/dL	Adults and children: 15 mg/kg/d
	Children: 20 mg/kg/d divided BD-QID	Rash	Urine Cu 250–500 μg/24 h	
		Lupus-like reactions Bone marrow suppression Nephrotic syndrome Colitis (rare) Note: requires supplemental pyridoxine, and dose reduction for surgery and pregnancy		
Trientene	Adults: 750–1500 mg divided TID-QID	Sideroblastic anemia	Same free Cu as above	Adults and children: 15 mg/kg/d
	Children: 20 mg/kg/d divided TID-QID	Colitis (rare)	Urine Cu 100–500 μg/24 h	
Zinc salts	(Dosing is in milligrams of *elemental* zinc)	GI intolerance	Same as above; plus, urine zinc >1000 μg/24 h	Adults: 75–150 mg divided TID
	Adults: 150 mg divided TID	Nonpancreatitis elevation of amylase and lipase		Children: 50–75 mg divided TID
	Children (<50 kg): 75 mg/d divided TID			

BD, daily; BID, twice daily; QID, four times daily; TID, three times daily; GI, gastrointestinal.
Adapted from Schilsky ML, Tavil AS. Wilson disease. In: Schiff's Diseases of the Liver. Philadelphia: Lippincott Williams and Wilkins; 2006:1023–1040.
Most practitioners prefer start with trientine. Zinc salt monotherapy or lower dose chelation is preferred for maintenance therapy.

Rosencrantz R et al, Semin Liver Dis 2011

WD Treatment: D-Penicillamin

- **First orally effective copper chelation therapy** developed for WD; has the most published clinical experience: **Promotes urinary excretion of copper**
- Despite known toxicities and the availability of newer regimens, D-Penicillamine is still the **drug of choice** in most of the centres for treatment of WD (hepatic and neurologic presentations)
- **Initial: 1 g/day in 2-4 divided doses**. Can be increased to 1.5-2 g/day in an overtly ill patient failing to show clinical improvement
- **Maintenance: 750-1500 mg/day in 2-3 divided doses**
- **Pediatric dose: 20 mg/Kg/day** in 2-4 divided doses
- Best **given 1 hr prior or 2-3 hrs after meals** as food inhibits its absorption
- Best **to start at low dose** with subsequent increments for better tolerability

WD Treatment: D-Penicillamin

- Pyridoxine therapy: D-Penicillamine may have an antipyridoxine effect, thus all patients are recommended **25-50 mg of pyridoxine weekly**
- **Interactions/Contraindicated:** Cidofovir, Streptozocin
- **Interactions/Avoid:** Aminoglycosides, Chloroquine phosphate, Gold compounds, Tenofovir, Probenecid, Clofarabine, Magnesium salts, Iron salts
- **Pregnancy:** Treatment should be **continued throughout the course of pregnancy**. Interruption of chelation therapy during pregnancy can result in acute liver failure or decompensation. **Dose reduction is advised**.
- **Lactation:** Women taking D-Penicillamine **should not breast feed** as the drug is excreted into breast milk and could potentially be harmful to the infant
- **Reduce dose for surgery to promote wound healing**

WD Treatment: D-Penicillamin Side Effects

- **Fever, rash, lupus like reaction** (may need discontinuation of therapy)
- **Bone marrow toxicity** resulting in thrombocytopenia, leukopenia or aplastic anemia- close monitoring required, significant bone marrow toxicity necessitates discontinuation of treatment
- **Proteinuria:** monitor through urinalysis every week initially and then 1-3 monthly
- **Late toxic reactions** include nephrotic syndrome, Goodpasture's syndrome, agranulocytosis, optic neuritis, myasthenia gravis, drug-induced systemic lupus erythromatosus: discontinuation of the drug necessary
- **Dermatological toxicities** including cutis laxa, elastosis perforans serpiginosa, lichen planus: temporary discontinuation or consider alternative therapy
- **Hepatotoxicity:** temporary discontinuation or consider alternative therapy
- **Worsening of neurologic symptoms** during the initial phase of treatment: start with incremental doses and build up slowly

WD Treatment: Zinc

- **Induces intestinal metallothionein, thus reducing copper absorption**
- Currently **mainly used for maintenance therapy**
- EASL guidelines (2012) recommend to reserve this drug for patients with neurologic disease only
- **Adult dose: 75-250 mg/day** on an empty stomach, to be taken at least 2 hrs from chelator if on combination therapy
- **Pediatric dose: 25 mg of elemental zinc 3 times/day for children** <50 Kg, dosage not well established for children under 5 years
- No significant drug interactions known
- Side effects: **Gastric irritation** (certain salts cause less irritation e.g. Acetate and gluconate may be better tolerated than sulphate), elevation of pancreatic **lipase** and **amylase**, **hepatic deterioration**, possible impairment in immune function

WD Treatment Monitoring: Non-ceruloplasmin-bound copper

- The **non-ceruloplasmin-bound copper** is a fraction that is **typically ~10%** of the **total serum copper**
- Amount of non-ceruloplasmin copper is estiamted by simultaneously measuring serum ceruloplasmin and total serum copper (online copper calculator)
- In an **untreated WD** patient, the percentage of non-ceruloplasmin copper rises to over **25 – 50%** and may **exceed 25 µg/dL**
- **Effective medical treatment** is the lowering of the fraction of non-ceruloplasmin-bound copper to the **normal range of 10–15 µg/dL**
- **Maintenance therapy**: lower target range of **~10 µg/dL** should be maintained
- When non-ceruloplasmin levels drop far below 10 µg, patients may experience further reduction in serum levels of ceruloplasmin and ferroxidase activity with resultant anaemia and, in some, the development of hepatic haemosiderosis

WD Treatment Monitoring: Urinary copper excretion

- Urinary copper excretion may be used to gauge the effectiveness of treatment
- **Following initial treatment** with chelating agents, 24-h urine copper excretion **typically rises above 500 µg/24 h**
- With **ongoing treatment**, the urinary copper excretion falls, typically ranging between **250 and 500 µg/24 h**
- For **chronically treated patients**, values **less than 250 µg/24 h** suggest either depletion of copper stores or non-adherence to therapy
- The simultaneous estimation of **non-ceruloplasmin copper** by serum testing may help to **distinguish between depletion and non-adherence**, the former with values < 10 µg/dL while the latter are typically elevated above 25 µg/dL.

WD Treatment: D-Penicillamin Monitoring

Lab Tracker and Copper Calculator

Serum Copper (mcg/dl)	Ceruloplasmin (mg/dl)	Non-Ceruloplasmin Copper	Calculate
Serum Copper (micromoles/liter)	Ceruloplasmin (mg/L)	Non-Ceruloplasmin Copper	Calculate
Copper Concentration (micromoles/liter)	Volume (liters)	Copper per 24 hours (microgram)	Calculate
Copper concentration (mcg/dl)	Volume (liters)	Copper per 24 hours (microgram)	Calculate
Copper concentration (mcg/liter)	Volume (liters)	Copper per 24 hours (microgram)	Calculate
Zinc concentration (mcg/liter)	Volume (liter)	Zinc per 24 hours (microgram)	Calculate

WILSON DISEASE ASSOCIATION INTERNATIONAL

http://www.wilsonsymptom.com/wilsondisease/labtracker-coppercalclulator.php

TREATMENT AND MONITORING OF WILSON DISEASE

Name	Units	Reference Range	Date:	Date:	Date:	Date:	Date:
Medications							
d-Penicillamine	mg/day						
Pyridoxine (B6)	mg/day						
Trientine	mg/day						
Zinc	mg/day						
Zinc (other)	mg/day						
Other medications							
CBC/Platelets							
WBC							
Hgb							
HCT							
Platelets							
Liver Function Panel							
Albumin							
Total bilirubin							
Direct bilirubin							
Alkaline phosphatase							
ALT							
AST							
Alpha fetoprotein (AFP)							
Coagulation							
INR							
Prothrombin time							
Copper and Zinc Parameters							
Serum copper							
Serum ceruloplasmin							
24 hour urine (copper/volume)							
24 hour urine zinc							
Non-ceruloplasmin copper							
Urinalysis							
Protein							
WBC							
RBC							
Other							
BUN							
Creatinine							
Neurological Symptoms							
Absent	X						
Present	X						
Tremors	I NI W						
Speech (dysarthria)	I NI W						
Coordination	I NI W						
Swallowing	I NI W						
Incontinence	I NI W						
Other							
Psychiatric Symptoms							
Absent	X						
Present	X						
Anxiety	I NI W						
Depression	I NI W						
Mood swings	I NI W						
Other							

Supportive measures: Avoid food with high copper content

USDA National Nutrient Database for Standard Reference, Release 21
Copper, Cu (mg) Content of Selected Foods per Common Measure, sorted by nutrient content

NDB_No	Description	Weight (g)	Common Measure	Content per Measure
13327	Beef, variety meats and by-products, liver, cooked, pan-fried	85	3 oz	12.400
15167	Mollusks, oyster, eastern, wild, raw	84	6 medium	3.740
15168	Mollusks, oyster, eastern, cooked, breaded and fried	85	3 oz	3.650
15148	Crustaceans, lobster, northern, cooked, moist heat	85	3 oz	1.640
11269	Mushrooms, shiitake, cooked, without salt	145	1 cup	1.299
19062	Snacks, trail mix, regular, with chocolate chips, salted nuts and seeds	146	1 cup	1.232
19080	Candies, semisweet chocolate	168	1 cup	1.176
15141	Crustaceans, crab, blue, canned	135	1 cup	1.026
15137	Crustaceans, crab, alaska king, cooked, moist heat	85	3 oz	1.003
11546	Tomato products, canned, paste, without salt added	262	1 cup	0.958
19078	Baking chocolate, unsweetened, squares	28.35	1 square	0.917
20005	Barley, pearled, raw	200	1 cup	0.840
11261	Mushrooms, cooked, boiled, drained, without salt	156	1 cup	0.786
22247	Macaroni and Cheese, canned entree	252	1 cup	0.746
19061	Snacks, trail mix, tropical	140	1 cup	0.739
12187	Nuts, chestnuts, european, roasted	143	1 cup	0.725

i.e. Avoid liver, crab meat, nuts, broccoli, mushrooms, chocolate.

If the copper concentration in water is over 0.1 ppm (parts per million = 0.1 mg/L) an alternative source is recommended

United States Department of Agriculture National Nutrient Database for Standard Reference www.ars.usda.gov

WD Treatment (4): Liver Transplantation

- **Transplantation is frequently necessary** for patients presenting with **acute liver failure or decompensated cirrhosis**
- **Eligible for Super Urgent Transplantation List** in case of fulminant presentation
- Because the biochemical defect resides mainly in the liver, liver transplantation corrects the **genetic defect**
- Survival rates are similar to other liver diseases
- Survival after transplantation is better for chronic advanced liver disease presentation than for acute liver failure
- Living related donor liver transplantation from a heterozygote donor is feasible

References

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Wilson's disease

European Association for the Study of the Liver*

www.easl.eu

www.wilsonsdisease.org

www.wilsonsymptom.com/wilsondisease/labtracker-coppercalclulator.php

Rosencrantz R et al. „Wilson disease: pathogenesis and clinical considerations in diagnosis and treatment", *Semin Liver Dis 2011*