

## Wilson Disease

### Clinical Background

Wilson disease (also called hepatolenticular degeneration, Westphal-Struempell disease, Westphal pseudosclerosis) is an autosomal recessive inherited disorder of copper metabolism.

#### Epidemiology

- Incidence – 1/30,000
- Age – onset of symptoms <40 years
- Sex – M:F, equal

#### Inheritance

- Caused by mutation in the *ATP7B* gene (located on chromosome 13)
- Autosomal recessive transmission
  - ~1% of population are carriers

#### Pathophysiology

- Ceruloplasmin, a late acute phase reactant, is the principal copper-containing protein of plasma and is transported into the trans-Golgi network of all cells by copper-transporting ATPases
- Disease results from the absence or dysfunction of copper-transporting ATPases
- Variant P-type ATPase prevents incorporation of copper into ceruloplasmin resulting in elevated concentrations of circulating free copper
- Excess copper is deposited in the kidneys, liver (causes cirrhosis), eyes (Kaiser-Fleischer rings) and brain (damages the basal ganglia)
- Other conditions that prevent the elimination of copper (eg, biliary obstruction) may also lead to elevated free copper concentrations

#### Clinical Presentation

- Ophthalmic manifestations
  - Kayser-Fleischer rings (copper deposit on corneal Descemet membrane)
    - Seen in 50-60% of patients
    - Not specific for Wilson disease – can also be seen in chronic cholestasis
    - Presence does not correlate with severity
- Hepatic manifestations – hepatomegaly, fatty liver, hepatitis, cirrhosis
- Neurologic manifestations – movement disorders
  - Typically develop in the 20s and affect 40-50% of patients
  - Dystonia, tremor, incoordination
  - Bulbar and pseudobulbar palsies with hypokinetic speech and dysphagia
- Psychiatric manifestations
  - Behavioral disturbances, depression, hallucinations, paranoia
  - Frequently occur prior to hepatic and neurologic symptoms
- Complications
  - Hematologic – hemolytic anemia
  - Musculoskeletal – arthritis, osteoporosis
  - Renal – nephrolithiasis, aminoaciduria
  - Cardiac – cardiomyopathy, arrhythmias
  - Endocrine – hypoparathyroidism, infertility

### Treatment

- Goal of therapy is to reduce copper accumulation; prompt diagnosis is crucial as treatment requires 3-6 months for the desired effect
- Untreated Wilson disease can be fatal – result of fulminant liver failure and/or brain damage

### Diagnosis

- Indications for testing
  - Unexplained liver disease in patients <40 years of age
  - Unexplained neurological disease, especially in concert with liver disease
  - Kayser-Fleischer rings on ophthalmic exam
  - Family history of the disease in first-degree relative
- Laboratory testing
  - Pattern of results consistent with Wilson disease is most useful for diagnosis
    - Ceruloplasmin – decreased (<200 mg/L is highly suggestive of disease)
    - Serum free copper – increased (>25 mg/dL is diagnostic)
    - Urine (24 hour) copper – increased (>100 µg/24-hours is considered diagnostic)
    - Hepatic function – transaminases may be elevated; however, not useful in diagnosis
- Histology
  - Liver biopsy – increased copper concentrations (>250mg/g dry weight is diagnostic)
    - Copper content may be less in cirrhotic liver because of uneven distribution of copper in parenchyma
- Imaging studies
  - MRI is most useful – increased signal intensity in the basal ganglia on T2 weighted images

### Differential Diagnosis

- Hepatic manifestations
  - Viral hepatitis – hepatitis A, B, C or D
  - Chronic hepatitis – hepatitis B or C, autoimmune hepatitis
  - Chronic cholestasis – primary sclerosing cholangitis, primary biliary cirrhosis
- Neurologic manifestations
  - Degenerative cerebellar or metabolic diseases
  - Demyelinating disease – amyotrophic lateral sclerosis (ALS)
  - Metabolic storage disease – Gaucher disease
  - Vasculitis – microscopic polyangiitis, Churg-Strauss syndrome, polyarteritis nodosa
  - Central nervous system infections – viral, bacterial, parasitic, fungal
  - Seizure disorder
  - Parkinson's disease
  - Transverse myelitis
- Psychiatric
  - Psychoses
  - Depression
  - Schizophrenia

### Screening

- Genetic testing – consider testing for ATPase (*ATP7B*) genetic mutation
  - Negative result does not exclude Wilson disease

## Monitoring

- Measuring serum free copper is useful in monitoring therapy effectiveness

## Lab Tests

### Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
Wilson Disease Screening Panel, Serum <b>0020598</b> Method: Immunoturbidimetric/ Inductively Coupled Plasma/Mass Spectrometry	Diagnose conditions of copper overload in symptomatic patients and/or patients with a family history of Wilson disease  Panel includes serum ceruloplasmin, serum copper and free serum copper  Supports diagnosis of Wilson disease and monitors therapy in patient with Wilson disease	See individual component tests  Ceruloplasmin false positives may reflect malabsorption, aceruloplasminemia, liver insufficiency, heterozygotes for Wilson disease, inflammatory conditions	
Copper, Urine <b>0020461</b> Method: Inductively Coupled Plasma/Mass Spectrometry	Support diagnosis of Wilson disease	False positives from hepatocellular necrosis	
Copper, Liver <b>0020694</b> Method: Inductively Coupled Plasma/Mass Spectrometry	Support diagnosis of Wilson disease	False positives from alcoholic hepatitis, cholestatic syndromes	
Copper, Serum Free (Direct) <b>0020596</b> Method: Inductively Coupled Plasma/Mass Spectrometry	Supports diagnosis of Wilson disease and monitors therapy in patient with Wilson disease	Performed with serum ultrafiltrates  Elevated in Wilson disease or other conditions of copper overload  Elevated results should be confirmed with a second specimen to exclude the possibility of external contamination	

<p>Ceruloplasmin <b>0050160</b></p> <p>Method: Immunoturbidimetric</p>	<p>Supports diagnosis of Wilson disease</p>	<p>Positive result may not necessarily indicate Wilson disease because decreased ceruloplasmin levels may also be found in inflammatory conditions</p> <p>Pregnancy and oral contraceptives increase ceruloplasmin levels</p> <p>Low ceruloplasmin levels also found in malnutrition, malabsorption, nephrosis, severe liver disease</p>	
<p>Hepatic Function Panel <b>0020416</b></p> <p>Method: Refer to individual components.</p>	<p>Supports diagnosis of Wilson disease</p> <p>Panel includes albumin; alkaline phosphatase; aspartate aminotransferase; alanine aminotransferase; bilirubin, direct; protein, total; bilirubin, total</p>		

**Additional Tests Available**

Test Name and Number	Comments
<p>Copper, Serum <b>0020096</b></p> <p>Method: Inductively Coupled Plasma/Mass Spectrometry</p>	<p>Test available alone or as part of Wilson disease serum screening panel that also includes serum ceruloplasmin and serum free copper</p> <p>False positives from infection, inflammation, stress, copper supplementation, oral contraceptives, pregnancy</p> <p>Pregnancy – concentrations are 2-3 times normal in third trimester</p> <p>Copper may be lowered by corticosteroids, zinc, malnutrition, malabsorption</p>

**Guidelines**

Diagnosis and treatment of Wilson disease: an update. American Association for the Study of Liver Diseases - Private Nonprofit Research Organization. 2003 June (Revised 2008 June).

Roberts EA, Schilsky ML. A practice guideline on Wilson disease. *Hepatology*. 2003; 37 (6) :1475-1492.

**General References**

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Ferenci P. Wilson's Disease. *Clin Gastroenterol Hepatol*. 2005; 3 (8) :726-733.

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McMillin GA, Travis JJ, Hunt JW. Direct measurement of free copper in serum or plasma ultrafiltrate. *Am J Clin Pathol*. 2009; 131 (2) :160-165.

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### Diagnostic Algorithm(s)

PDF algorithm(s) available at [www.arupconsult.com](http://www.arupconsult.com).

Wilson Disease Testing Algorithm

### Related Content

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Cirrhosis

Hemochromatosis

Hepatitis B Virus - HBV

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Hepatitis, Autoimmune - AIH

Hepatocellular Carcinoma

Liver Disease Evaluation

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