

## Wilson's Disease (Hepatolenticular Degeneration) — Staging and Treatment

[See online here](#)

**Wilson disease is an autosomal recessive inherited disorder related with copper metabolism. This rare condition is characterized by excessive deposition of copper in target organs like liver, brain, and other tissues.**



### Background of Wilson's Disease

Is a **genetic defect** in chromosome 13q, which disrupts the copper-transporting adenosine triphosphatase gene (ATP7B). Patients often initially present with liver-related clinical features and more neurologic manifestations later. Wilson's disease is rare but important because it can be fatal if not recognized and treated opportune.

### Staging of Wilson's Disease

Wilson's disease consists of the following stages:

- Stage I - Accumulation of copper inside hepatic binding sites.
- Stage II - Redistribution of copper in the liver and its release into the circulation.
- Stage III - Chronic accumulation of copper in the brain and other tissues.
- Stage IV - Restoration of copper balance with treatment.

# Epidemiology of Wilson's Disease

- Worldwide:
  - Incidence - 10-30 million cases.
  - Heterozygote carrier rate - 1 case per 100 individuals.
  - Genetic mutation frequency - 0.3-0.7%.
  - Fulminant presentation - More common in females.
- United States:
  - Heterozygote carrier rate - 1 per 90 individuals.
  - Prevalence - 1 per 30,000 individuals.
- Japan
  - Prevalence - 1 case per 30,000 individuals
- Australia
  - Prevalence - 1 case per 100,000 individuals.

## Age-related presentation

Usually, the upper age limit is 40 years and the lower age limit is 5 years. However, it can also appear in children younger than 3 years and in adults older than 70 years.

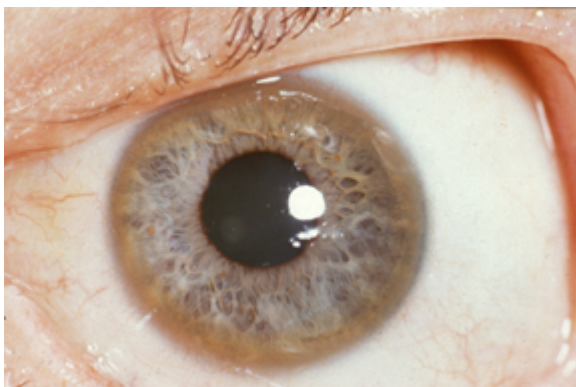
Always think about Wilson's disease in a young patient with a movement disorder or atypical psychiatric presentation.

## Clinical Features of Wilson's Disease

### History

Clinical symptoms vary from an **asymptomatic state** to **hepatic failure, chronic liver disease** with or without cirrhosis, **neurologic, and psychiatric symptoms**. Always consider this differential diagnosis in patients with unexplained chronic liver disease, particularly between 5-40 years. The three major patterns of hepatic involvement are: **chronic active hepatitis, cirrhosis**, and **fulminant hepatic failure**.

### Neuropsychiatric symptoms



**Image:** "Kayser-Fleischer ring: copper deposition in Descemet's membrane of the cornea. These rings can be either dark brown, golden, or reddish-green, are 1 to 3 mm wide, and appear at the corneal limbus. With rare exceptions, they are diagnostic of inherited hepatolenticular degeneration—Wilson's disease. This 32-year-old patient complained of longstanding difficulty speaking. He also had a tremor." by Herbert L. Fred, MD, Hendrik A. van Dijk -

50% of patients with Wilson's disease have neuropsychiatric symptoms and most of them have cirrhosis. Half present with **asymmetrical tremor** – predominantly resting, postural, or kinetic. **Kayser-Fleischer rings** are seen in 98% of patients with neurological Wilson's disease when not treated. Early symptoms also include difficulty with speaking, excessive salivation, ataxia, mask-like facies, clumsiness with the hands, and personality changes. Late manifestations include dystonia, spasticity, grand mal seizures, rigidity, and flexion contractures.

There are 4 different diagnostic categories based on neurologic findings:

- **Parkinsonian group** (45%) – paucity of expression and movement
- **Pseudosclerotic group** (24%) – tremor resembling [multiple sclerosis](#)
- **Dystonic group** (15%) – hypertonicity with abnormal limb movements
- **Choreic group** (11%) – choreoathetoid abnormal movements with dystonia.

10%-20 of patients with Wilson's disease have psychiatric symptoms like emotional lability, impulsiveness, disinhibition, and self-injurious behavior, divided into 4 basic categories:

- Behavioral
- Affective
- Schizophrenic-like
- Cognitive.

### **Musculoskeletal symptoms**

More than half of individuals exhibit **osteopenia** on conventional radiologic examination. The **arthropathy** is degenerative, 20-50% of patients show **joint affectation** late in the course of the disease. The arthropathy involves the spine and large appendicular joints, such as knees, wrists, and [hips](#). Also, osteochondritis dissecans, chondromalacia patellae, and chondrocalcinosis have been reported.

### **Hematologic symptoms**

[Hemolytic anemia](#) (10-15%), Coombs-negative acute intravascular hemolysis in higher copper concentrations. Wilson's disease must be considered in any patient with **acute hepatic failure, Coombs-negative intravascular hemolysis**, modest raises in serum aminotransferases, and low serum alkaline phosphatase or ratio of alkaline phosphatase to bilirubin less than 2.

### **Renal symptoms**

Wilson's disease gene is also expressed in kidney tissue, therefore the frequency of renal manifestations is variable and any renal manifestations may be primary or secondary to release of copper from the liver. It may resemble **Fanconi syndrome**, indicating defective renal acidification and excess renal losses of amino acids, glucose, fructose, galactose, pentose, uric acid, phosphate, and calcium.

Up to 16% of patients have **urolithiasis** as a result of hypercalciuria or poor acidification. **Hematuria** and **nephrocalcinosis** are described. **D-penicillamine treatment** may produce proteinuria and peptiduria as a side effect.

### **Fulminant Wilson disease**

Low serum transaminases, low serum alkaline phosphatase, hemolysis, and renal Fanconi syndrome are indicative of fulminant Wilson's disease.

# Physical Examination



Image: "Clubbing fingers" by Desherinka - Own work. License: [GNU Free Documentation License](#)

## Hepatic signs

- Ascites and prominent abdominal veins
- Spider nevi
- Palmar erythema
- Digital clubbing
- Hematemesis
- Jaundice

## Neurologic signs

- Drooling
- Dysphagia
- Dystonia
- Incoordination
- Difficulty with fine motor tasks
- Masklike facies
- Gait disturbance

## Ophthalmologic signs

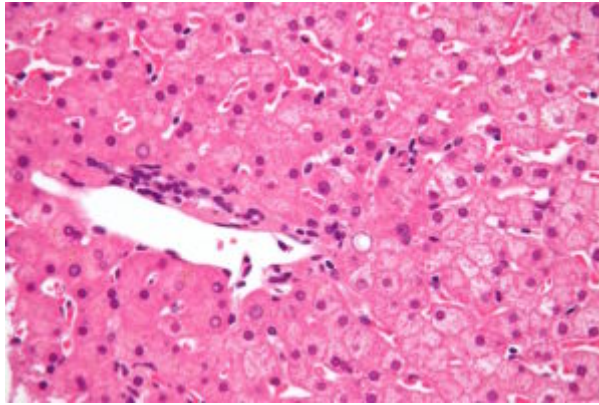
- Kayser-Fleischer rings
- Sunflower cataract

## Additional symptoms

[Osteoporosis](#), osteomalacia, [rickets](#), spontaneous fractures, and polyarthritis, [cardiac rhythm abnormalities](#), increased autonomic tone, hypertrophy, small vessel disease, and focal inflammation, [anemia](#), skin pigmentation and a **bluish discoloration at the base of the fingernails** (azure lunulae).

## Differential Diagnoses of Wilson's Disease

- [Acute Liver Failure](#)
- Arthritis from different etiology
- Hemochromatosis
- Hepatitis A, B, C, D, E



**Image:** "High magnification micrograph of ground glass hepatocytes, as seen in a chronic hepatitis B infection with a high viral load. Liver biopsy. H&E stain." by Nephron - Own work. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

- Schizophrenia
- Viral Hepatitis
- Autoimmune chronic active hepatitis
- Aceruloplasminemia
- Glycogen-storage disease type 0, I, II, III, IV, V, VI, VII
- Hepatocellular adenoma
- Cirrhosis
- [Multiple sclerosis](#)
- [Huntington disease](#)
- Depression
- Antisocial personality disorder
- [Parkinson disease](#)
- Leukodystrophy
- CNS vasculitis
- Leigh disease
- Neurodegenerative disease
- [α1-antitrypsin deficiency](#)
- Chronic anemia
- [Hereditary hemochromatosis](#)

## Workup of Wilson's Disease

**Kayser-Fleischer rings** and **ceruloplasmin less than 20 mg/dL** with **neurologic symptoms** suggest Wilson's disease. An isolated liver disease with hepatic copper concentration of more than 250 mg/g of dry weight and a low serum ceruloplasmin level is enough to establish the diagnosis of Wilson's disease. A **liver biopsy for quantitative copper determination** helps to establish the definitive diagnosis.

## Genetic diagnosis

First- and second-degree relatives of patients with confirmed Wilson's disease must be screened.

## Abdominal imaging

Computed axial tomography (CAT), magnetic resonance imaging (MRI), ultrasonography, and nuclear medicine studies of the liver have findings neither specific nor sensitive for

Wilson's disease.

## Electrocardiography

Electrocardiography may show left ventricular or biventricular hypertrophy, early repolarization, ST segment depression, T-wave inversion, and [arrhythmia](#).

## Serum ceruloplasmin

90% of individuals with Wilson's disease have ceruloplasmin levels of less than 20 mg/dL (reference range, 20-40 mg/dL). Heterozygous individuals may show decreased ceruloplasmin levels (10-20%) and may not develop the disease or require treatment.

## Urinary copper excretion

The urinary copper excretion rate may be useful to confirm the diagnosis and to evaluate the response to chelation therapy but the sensitivity and the specificity of this test are suboptimal. The rate is greater than 100 mcg/d (reference range, <40 mcg/d) in most patients with symptomatic Wilson's disease.

## Hepatic copper concentration

A liver biopsy reveals a copper concentration of more than 250 mcg/g of dry weight. A normal hepatic copper concentration (reference range, 15-55 mcg/g) excludes Wilson's disease. Other chronic hepatic disorders may produce elevated hepatic copper concentration.

## Radio-labeled copper

Radio-labeled copper testing analyses hepatic copper metabolism with blood collected at 1, 2, 4, 24, and 48 hours after oral ingestion of radio-labeled copper ( $^{64}\text{Cu}$  or  $^{67}\text{Cu}$ ). Radioactivity promptly appears after absorption, followed by hepatic clearance. In healthy people, the reappearance of the radioactivity in serum occurs as the labeled copper is incorporated into newly synthesized ceruloplasmin and released into the circulation. Patients with Wilson disease do not exhibit a secondary rise in radioactivity.

## Cranial CT scanning

Cranial lesions are classified in two categories: well-defined, slitlike, low-attenuation foci involving the basal ganglia, particularly the putamen; and larger regions of low attenuation in the basal ganglia, thalamus, or dentate nucleus.

## Brain MRI

Brain MRI is more sensitive than CT scanning in detecting early lesions of Wilson's disease. MRI studies have identified focal abnormalities in the white matter, [pons](#), and deep cerebellar nuclei, measuring 3-15 mm in diameter, typically bilateral representing cell loss and gliosis.

## PET scanning

Positron emission tomography (PET) scanning exposes a reduced regional cerebral metabolic rate of glucose consumption in the cerebellum, striatum, and, to a lesser

extent, in the cortex and thalamus.

## Electron microscopy

Studies on ultrathin sections reveal numerous electron-dense lysosomes and residual bodies.

## Hepatic histologic findings

The earliest changes detectable with light microscopy include glycogen deposition in the nuclei of periportal hepatocytes and moderate fatty infiltration. The lipid droplets, composed of triglycerides, progressively increase in number and size, sometimes similar to the steatosis induced by ethanol.

## Neurologic histologic findings

Anatomical changes include degeneration and cavitation in the putamen, globus pallidus, caudate nucleus, and thalamus. These areas do not possess especially high copper concentrations.

## Treatment and Management of Wilson's Disease

Pharmacologic treatment with chelating agents such as **D-penicillamine** and **trientine** is the gold standard. **Sodium dimercaptosuccinate**, **dimercaptosuccinic acid**, **zinc**, and **tetrathiomolybdate** are other options which favor a negative copper balance. The patient needs to be aware of potential adverse effects of the agents, commonly associated with penicillamine use.

**Surgical decompression** or **transjugular intrahepatic shunting (TIPS)** for [portal hypertension](#) is reserved for individuals with recurrent or uncontrolled [variceal bleeding](#) unresponsive to conservative treatment. With clinical progression, acute liver failure, or worsening hepatic function, the patient must be evaluated for [liver transplantation](#), as a curative treatment for Wilson disease.

## Diet

The patient should avoid eating foods with a high copper content, such as liver, chocolate, nuts, mushrooms, legumes, and shellfish. Drinking water from atypical sources should be analyzed for copper content and replaced with purified water with copper content less than 0.2 parts per million.

## Pregnancy

Excessive intrauterine copper concentrations may be responsible for spontaneous abortions in patients with Wilson's disease. Treatment with D-penicillamine (0.75-1.5 g/day) poses no major risk to the fetus.

## Pediatric

Pediatricians should consider Wilson's disease in any child with hepatic abnormalities which requires pediatric gastroenterologist consultation if suspicion remains high.

## Geriatric

Patients with Wilson's disease who are untreated in the geriatric age will most likely present with [fulminant hepatic failure](#) or with signs and symptoms of cirrhosis.

## Neurologic deterioration with treatment

Some patients may develop worsening neurologic symptoms when therapy is initiated. In these cases, the chelating agent may need to be stopped and the patient should be treated only **zinc acetate**. Patients on long-term treatment require regular follow-up to monitor for disease progression.

## References

[Wilson Disease](#) via medscape.com

[Wilson's disease](#) via mayoclinic.org

[Wilson's disease](#) via wikipedia.org

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Notes