

# Wilson Disease

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## Overview

- [What is Wilson disease?](#)

Wilson disease is an inherited disorder that causes too much copper to accumulate in the liver, brain, and other vital organs. Copper plays a key role in the development of healthy nerves, bones, collagen and the skin pigment. A small amount of copper obtained from food is needed to stay healthy, but too much copper is poisonous. In Wilson disease, a genetic defect prevents the body from getting rid of extra copper. Wilson disease is named after Dr Samuel Alexander Kinnier Wilson (1878-1937), the British neurologist who first described the condition in 1912.

- [What causes Wilson disease?](#)

Normally, copper is absorbed from food, and any excess is excreted through bile, a substance produced in the liver, which flows out of the body through the gut. People who have Wilson disease cannot release copper from the liver at a normal rate, due to a mutation in the gene on chromosome 13 that contains the blueprint for the Wilson disease protein (ATP7B), which helps transport copper into the bile. The copper accumulates in the liver, sometimes to toxic levels and when the copper storage capacity of the liver is exceeded, copper is released into the bloodstream and travels to other organs—including the brain, kidneys, and eyes.

- [Who gets Wilson disease?](#)

Individuals who carry one normal copy and one abnormal copy of the ATP7B gene do not develop any symptoms (they are carriers). If a child inherits the abnormal gene from both parents, they may develop Wilson disease. The inheritance pattern of Wilson disease is autosomal recessive. Wilson disease occurs on an average in about 1 per 30,000 people worldwide. Most people with Wilson disease have no known family history of the disease. A person's chances of having Wilson disease increase if one or both parents have Wilson disease. If both parents carry an abnormal gene for Wilson disease, there is a 25% chance in each pregnancy that the child will have the disorder.

Wilson disease affects men and women equally. It is most common in eastern Europeans, Sicilians, and southern Italians, but may occur in any ethnic group.

- [What are the symptoms of Wilson disease?](#)

Symptoms usually appear between ages 5 to 35, but new cases have been reported in people aged 2 to 72 years. Liver failure and damage to the central nervous system (brain, spinal cord) are the most predominant, and the most dangerous, effects of the disorder. If not caught and treated early, Wilson disease can be fatal.

Patients with liver problems tend to come to medical attention earlier, generally as children or teenagers, than those with neurological and psychiatric symptoms, who tend to be in their twenties or older. Some are identified only because relatives have been diagnosed with Wilson disease; many of these patients, when tested, turn out to have been experiencing symptoms of the condition but have not been diagnosed with it.

A buildup of copper in the liver may cause ongoing chronic liver disease, which can progress to cirrhosis (scarring of the liver). Most patients develop signs and symptoms that accompany chronic liver disease, including fatigue, abdominal pain and yellowing of the skin and whites of the eyes (jaundice). Later in the disease, bleeding in the gut, which can show up either as vomiting of red blood or black colored stools (melena) can occur. Other signs and symptoms may include swelling due to fluid buildup in the abdomen (ascites) or legs (edema), an enlarged spleen and a tendency to bruise easily, and anemia. Confusion (hepatic encephalopathy) due to inability of the liver to clear toxins including ammonia can occur which can progress to coma. While most people with cirrhosis have an increased risk of liver cancer, this risk is relatively low in patients with Wilson disease.

Rarely, acute liver failure (rapid loss of liver function over days to weeks, without scarring of the liver) can occur. About 5% of all patients are diagnosed only when they develop acute liver failure. This leads to abnormalities in protein production and metabolism by the liver. The deranged protein production manifests as blood coagulation problems causing tendency to bleed easily all over the body. The deranged protein metabolism leads to the accumulation of waste products such as ammonia in the bloodstream. When these irritate the brain, the patient develops hepatic encephalopathy (confusion, coma, seizures and finally life-threatening swelling of the brain).

- **Neuropsychiatric symptoms:** About half of patients with Wilson disease have neurological or psychiatric problems. Most patients initially have mild cognitive deterioration and clumsiness, as well as changes in behavior, problems with speech, swallowing, or physical coordination, tremors or uncontrolled movements, muscle stiffness and spasms, unsteady gait and drooling. Seizures and migraine appear to be more common in Wilson disease. Wilson disease can cause abrupt personality changes and inappropriate behavior. Children with the disease are sometimes misdiagnosed as having behavioral problems because they behave erratically or perform poorly in school.
  
- **Eye, kidney and bone problems:** Many people with Wilson disease, even those who don't have other signs and symptoms, develop a distinctive, golden brown pigmentation around their corneas (Kayser-Fleischer ring). Caused by copper deposits, Kayser-Fleischer rings are often discovered during a routine eye exam. Wilson disease can also interfere with the filtering function of the kidneys and can lead to weak, brittle bones (osteoporosis). The disease can also lead to kidney stones.
  
- **Heart problems:** cardiomyopathy (weakness of the heart muscle) is a rare but recognized problem in Wilson disease; it may lead to heart failure (fluid accumulation due to decreased pump function) and cardiac arrhythmias (episodes of irregular and/or abnormally fast or slow heart beat).
  
- **Hormonal problems:** Copper accumulation can lead to hypoparathyroidism (failure of the parathyroid glands leading to low calcium levels), infertility and frequent spontaneous loss of a pregnancy (spontaneous abortion).
- [How is Wilson disease diagnosed?](#)

Wilson disease is diagnosed through a combination of physical examination and laboratory tests.

  - **Eye exam:** Using a microscope with a high-intensity light source (slit lamp), an ophthalmologist checks your eyes for Kayser-Fleischer rings. Kayser-Fleischer rings are present in almost all people with Wilson disease who show signs of neurologic damage but are present in only 50 percent of those with signs of liver damage alone.
  
  - **Blood and urine tests:** Laboratory tests are done to measure the amount of ceruloplasmin (the protein that transports copper in the blood) and copper in the blood, and to test the amount of copper excreted in the urine in a 24-hour period. Most people with Wilson disease will have a lower than normal level of copper in the blood and a lower level of corresponding ceruloplasmin. A 24-hour urine collection will show increased copper in the urine in most patients who display symptoms.
  
  - **Liver biopsy:** In this procedure, a small sample of tissue is removed from the liver and examined in a laboratory for excess copper. The analysis of biopsied liver tissue with a microscope detects liver damage, which often shows a pattern unique to Wilson disease.

If there are neurological symptoms, magnetic resonance imaging (MRI) of the brain is usually performed; this shows structural changes in the part of the brain called the basal ganglia.

There is no totally reliable test for Wilson disease, but levels of ceruloplasmin and copper in the blood, as well as the amount of copper excreted in the urine during a 24 hour period, are together used to form an impression of the amount of copper in the body. The combination of neurological symptoms, Kayser-Fleisher rings and a low ceruloplasmin level is considered sufficient for the diagnosis of Wilson disease. In many cases, however, further tests are needed. The “gold standard” or most ideal test is a liver biopsy.

Genetic testing may help diagnose Wilson disease in some people, particularly in those where a close relative has been found to have Wilson disease. A blood test called DNA mutation analysis is available at a limited number of medical centers but is not generally commercially available. This test can identify the genetic mutations that cause Wilson disease. Mutation analysis of the ATP7B gene, as well as other genes linked to copper accumulation in the liver, may be performed. Once a mutation is confirmed, it allows screening of asymptomatic family members for the disease and beginning treatment before debilitating symptoms arise. It must be remembered that whenever genetic testing is done, genetic counseling must be available and informed consent should be obtained.

- [What is the treatment of Wilson disease? \(Table 1\)](#)

Wilson disease is a very treatable condition. With proper therapy, disease progress can be halted and oftentimes symptoms can be improved. Left untreated, Wilson disease may be fatal.

Wilson disease requires lifelong treatment to reduce and control the amount of copper in the body. Once treatment starts, the disease stops progressing and many signs and symptoms improve. But some problems may take time to resolve. Other problems — especially liver scarring and certain neurological or psychological symptoms — may not be completely reversible.

Treatment is initially aimed at removing excess accumulated copper and subsequently to prevent its reaccumulation.

Initial therapy includes the removal of excess copper, a reduction of copper intake, and the treatment of any liver or central nervous system damage.

Excess copper is removed by means of chelating drugs, which are chemicals used to bind metals and minerals. These orally ingested drugs release copper from organs into the bloodstream, which is then filtered out by the kidneys and excreted in urine. The following drugs have been approved and used for treatment of Wilson disease.

- **Penicillamine (Cuprimine, Depen).** Penicillamine was the first copper chelating drug approved for use in Wilson disease. Although it is an effective treatment, penicillamine can cause serious side effects, including skin problems, bone marrow suppression, kidney problems, vitamin B-6 deficiency and worsening of neurological symptoms and birth defects.

Penicillamine should not be taken by people with kidney disease or by those who are allergic to penicillin.

- **Trientine (Syprine).** Another chelating agent, trientine also binds to copper and helps eliminate it from the body. Because it is less toxic than penicillamine, many doctors consider it a first-line therapy, especially in people with liver or neurological symptoms. Trientine also binds to iron, and taking iron supplements can reduce the drug's effectiveness.

A potential major side effect of both drugs is that neurologic symptoms can become worse—a possible result of the newly released copper becoming reabsorbed by the central nervous system.

- **Tetrathiomolybdate** is another chelating drug that is under investigation for initial treatment of Wilson disease. Thus far, it has not caused the neurological worsening often associated with penicillamine and even with trientine.

- **Zinc acetate.** Working differently from chelating drugs, the mineral zinc helps prevent copper from being absorbed in the gut. Zinc has few side effects, but it is slower acting than either penicillamine or trientine and so is usually considered an initial treatment only for pregnant women, for people without symptoms or liver damage, or for those who cannot tolerate stronger medications. Its role is mainly in maintenance therapy.
- **Maintenance therapy** begins when symptoms improve and tests show that copper has been reduced to a safe level. Maintenance therapy typically includes taking zinc and low doses of either d-penicillamine or trientine hydrochloride. Blood and urine should be monitored by a health care provider to ensure treatment is keeping copper at a safe level.

Liver transplantation is the last resort treatment and may be the only option in some scenarios. It is used mainly in patients with acute liver failure who fail to respond to medical treatment, or in patients with advanced chronic liver disease.

People with Wilson disease should reduce their dietary copper intake. They should not eat shellfish or liver, as these foods may contain high levels of copper. Other foods high in copper—including mushrooms, nuts, and chocolate—should be avoided during initial therapy but, in most cases, may be eaten in moderation during maintenance therapy. People with Wilson disease should have their drinking water checked for copper content and should not take multivitamins that contain copper. In patients with chronic liver disease due to Wilson disease, alcohol ingestion should be avoided.

If the disorder is detected early and treated effectively, people with Wilson disease can enjoy good health.

#### **Table 1. Treatment of Wilson Disease**

- Medications
  - Penicillamine
  - Trientine
  - Zinc acetate
  - Combinations of above
  - Tetrathiomolybdate – investigational
- Diet
  - Low copper
  - Liver transplantation

### **Author(s) and Publication Date(s)**

*Bruce R. Bacon, MD, FACP, and Sudhanshu Gogia, MD, Saint Louis University School of Medicine, St. Louis, MO – Published February 2011.*