Wilson's Disease

Chapter 427 | Part 12: Endocrinology and Metabolism | Part 12 – Endocrinology & Metabolism | DETAILED EDITION

KEY CLINICAL POINTS

1. Wilson's disease is an autosomal recessive inherited disorder of copper transport caused by loss-of-function variants in ATP7B.
2. The Kayser-Fleischer ring is a pathognomonic sign present in 95% of patients with neurologic signs and approximately two-thirds of those with hepatic presentations.
3. Diagnosis is confirmed by hepatic copper levels >200 µg per gram of dry weight (normal 20–50 µg) or a combination of clinical, biochemical, and molecular features.
4. Treatment involves copper chelation (penicillamine, triethylene tetramine) or zinc salts to reduce gastrointestinal copper absorption.
5. Liver transplantation is indicated for end-stage liver disease or patients unresponsive to medical therapies.
6. Hemolytic anemia can occur due to direct toxic effects of copper on red blood cell membranes, often associated with release of massive hepatic copper into circulation.
7. Neurologic signs reflect predilection for basal ganglia (caudate, putamen) involvement.
8. Newborn screening using ATP7B peptides may transform presymptomatic diagnosis in the future.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

Wilson's disease (hepatolenticular degeneration) is an autosomal recessive inherited disorder of copper transport that primarily impacts the liver and brain. It results from loss-of-function variants in ATP7B, a highly evolutionarily conserved P-type ion-motive ATPase that normally mediates copper removal from the liver via biliary excretion and prevents brain copper accumulation. The condition is arguably one of the best-characterized and most effectively managed human inborn errors of metabolism.

1.1 History of Wilson's Disease

• Wilson's disease was first described in 1912 by neurologist S.A.K. Wilson, who recognized the heritable aspect of the condition.

• In 1948, pathologist J.N. Cumings proposed an etiologic connection with copper overload.

• In 1956, copper chelation by d-penicillamine was introduced and found preferable to anti-lewisite (a metal chelator developed to counteract an arsenic-based chemical warfare agent) with respect to route of administration and side effect profile.

• In the early 1970s, triethylene tetramine became the second U.S. Food and Drug Administration (FDA)–approved treatment for Wilson's disease.

• In the early 1970s, the first liver transplants were performed for Wilson's disease, with resultant correction of hepatic failure and crippling neurologic impairments in patients unresponsive to medical therapies.

• In 1993, the gene for Wilson's disease was identified and found to encode a copper-transporting ATPase, ATP7B, expressed primarily in liver and kidney.

• Zinc salts to reduce gastrointestinal copper absorption were recognized in the early 1960s, eventually leading to FDA approval for this indication.

• Tetrathiomolybdate, which forms a tripartite complex with copper and albumin, and a bacterial peptide, methanobactin, which traverses mitochondrial membranes, are more recently proposed copper chelators with potential for treatment of Wilson's disease.

1.2 Phenotypes

• Presenting clinical features of Wilson's disease include nonspecific liver disease, neurologic abnormalities, psychiatric illness, hemolytic anemia, renal tubular Fanconi syndrome, and various skeletal abnormalities.

• Age influences the specific presentation in Wilson's disease.

• Nearly all individuals who present with liver disease are <30 years of age.

• Those presenting with neurologic or psychiatric signs may range in age from the first to the fifth decade.

• Regardless of clinical presentation, some degree of liver disease is invariably present.

• Wilson's disease may be mistakenly diagnosed as Parkinson disease or other movement disorders.

• Wilson's disease should be formally excluded in all teenagers and young adults with new-onset psychiatric signs.

2. EPIDEMIOLOGY

Population-based and genomic-based estimates of prevalence range from 1 in 7000 to 1 in 30,000, with genome-based ascertainments supporting the higher prevalence. This disparity may reflect incomplete penetrance, although there is little doubt that some affected individuals unfortunately escape medical attention.

2.1 Global Considerations

• The HFE mutation is of northern European origin (Celtic or Nordic) with a heterozygous carrier rate of ~1 in 10 (1 in 8 in Ireland).

• Thus, HFE-associated hemochromatosis is quite rare in non-European populations, e.g., Asia.

• However, non-HFE-associated hemochromatosis resulting from mutations in other genes involved in iron metabolism is ubiquitous and should be considered when one encounters iron overload.

• African iron overload occurs primarily in sub-Saharan Africa and was previously thought to be due to the consumption of an iron-rich fermented maize beverage.

• Recent evidence suggests that it is primarily the result of a non-HFE-related genetic trait that is exacerbated by dietary iron loading.

• A similar form of iron overload has been described in African Americans.

3. ETIOLOGY & PATHOPHYSIOLOGY

Wilson's disease is caused by loss-of-function variants in ATP7B. Despite similar genomic structures, large deletions are much less common in ATP7B than in ATP7A, the closely related X-linked gene responsible for Menkes disease. Several ATP7B missense variants are common (H1069Q, M645R, and R778L), with various allelic frequencies reflecting geographic, racial, and/or ethnic differences. Major ATP7B databases list >650 pathogenic or likely pathogenic variants.

3.1 Molecular Mechanism

- ATP7B is a copper-transporting ATPase expressed primarily in liver and kidney.
- It normally mediates copper removal from the liver via biliary excretion.
- It prevents brain copper accumulation.
- Variants or polymorphisms in other genes (e.g., CAT, SOD2, MTHFR) may influence clinical expression of Wilson's disease in some individuals.

3.2 Pathogenesis Cascade

- Loss of function leads to failure of copper removal from the liver via biliary excretion.
- Copper accumulates in the liver, causing hepatotoxicity.
- Excess copper is released into circulation, causing hemolytic anemia.
- Copper accumulates in the brain (basal ganglia), causing neurologic dysfunction.
- Copper accumulates in the cornea (Descemet membrane), causing Kayser-Fleischer ring.

4. CLINICAL FEATURES

Presenting clinical features of Wilson's disease include nonspecific liver disease, neurologic abnormalities, psychiatric illness, hemolytic anemia, renal tubular Fanconi syndrome, and various skeletal abnormalities. Age influences the specific presentation in Wilson's disease. Nearly all individuals who present with liver disease are <30 years of age, whereas those presenting with neurologic or psychiatric signs may range in age from the first to the fifth decade.

4.1 Hepatic Presentation

- Signs and symptoms include jaundice, hepatomegaly, edema, or ascites.
- Viral hepatitis and cirrhosis are often initial diagnostic considerations in individuals who, in fact, have Wilson's disease.
- Clinical signs include:
- Jaundice
- Anorexia
- Vomiting
- Ascites and/or edema
- Splenomegaly
- Fatty liver
- Cirrhotic liver
- Hypoalbuminemia
- Elevated liver enzymes

4.2 Neurologic Presentation

• Abnormalities include distinctive speech difficulties (dysarthria), dystonia, rigidity, tremor (e.g., wing-beating) or choreiform movements, abnormal gait, and uncoordinated handwriting.

• Wilson's disease can properly be classified as a movement disorder.

• The neurologic signs and symptoms reflect the predilection for basal ganglia (e.g., caudate, putamen) involvement in the brains of affected persons.

• Wilson's disease may be mistakenly diagnosed as Parkinson disease or other movement disorders.

• Clinical signs include:

• Dysarthria

• Facial grimace (risus sardonicus)

• Drooling

• Dysphagia

• Dysgraphia

• Dystonia

• Tremor (wing-beating)

• Ataxia

• Seizures (rare)

4.3 Psychiatric Presentation

• Changes in personality (irritability, anger, poor self-control) or school performance, depression, and anxiety are common symptoms.

• Typically, patients presenting in this fashion are in their late teens or early twenties, a period during which substance abuse is also a diagnostic consideration.

• Clinical signs include:

• Decline in school performance

• Personality change

• Mood disorder

• Schizophrenia

4.4 Ocular Manifestations

• The eye is a primary site of copper deposition in Wilson's disease, producing a pathognomonic sign, the Kayser-Fleischer ring.

• This important diagnostic sign first appears as a superior crescent, then develops inferiorly, and ultimately becomes circumferential.

• Slit-lamp or optical coherent tomography examinations are required to detect rings in their early stage of formation.

• Copper can also accumulate in the lens and produce sunflower cataracts (rare).

• Approximately 95% of Wilson's disease patients with neurologic signs manifest the Kayser-Fleischer ring compared to two-thirds of those with hepatic presentations.

• Copper chelation therapy causes fading and eventual disappearance of corneal copper.

4.5 Other Clinical Manifestations

• Secondary endocrine effects of Wilson-associated liver disease may include delayed puberty or amenorrhea.

• Renal tubular dysfunction in Wilson's disease leads to abnormal losses of amino acids, electrolytes, calcium, phosphorus, and glucose.

• Anorexia, vomiting, and ascites/edema are associated with hepatic involvement.

• Hemolytic anemia due to the direct toxic effects of copper on red blood cell membranes is usually associated with release of massive quantities of hepatic copper into the circulation, a phenomenon that can be sudden and catastrophic.

• Skeletal effects include osteoporosis and rickets, which may be attributable to renal losses of calcium and phosphorus.

• Osteoarthritis, primarily affecting the knees and wrists, may involve excess copper deposition in the bone and cartilage.

• Drooling is associated with neurologic dysfunction.

5. DIFFERENTIAL DIAGNOSIS

Wilson's disease should be formally excluded in all teenagers and young adults with new-onset psychiatric signs. Wilson's disease may be mistaken for Parkinson disease or other movement disorders. Viral hepatitis and cirrhosis are often initial diagnostic considerations in individuals who, in fact, have Wilson's disease. Hemochromatosis in a heavy drinker can be distinguished from alcoholic liver disease by the presence of the C282Y mutation. End-stage liver disease may also be associated with iron overload of the degree seen in hemochromatosis. The mechanism is uncertain, although studies have shown reduced hepcidin and intestinal iron transporter expression. Hemolysis also plays a role. HFE mutations are uncommon in alcoholic liver disease.

5.1 Wilson's Disease vs. Hemochromatosis

• HFE mutations are not increased in frequency in alcoholic liver disease.

• However, alcohol does reduce hepcidin expression, which accounts for increased iron absorption and hepatic iron sometimes seen in alcoholic liver disease.

• Hemochromatosis in a heavy drinker can be distinguished from alcoholic liver disease by the presence of the C282Y mutation.

• End-stage liver disease may also be associated with iron overload of the degree seen in hemochromatosis.

• The mechanism is uncertain, although studies have shown reduced hepcidin and intestinal iron transporter expression.

• Hemolysis also plays a role.

• HFE mutations are uncommon in alcoholic liver disease.

5.2 Wilson's Disease vs. Alcoholic Liver Disease

• Alcohol does reduce hepcidin expression, which accounts for increased iron absorption and hepatic iron sometimes seen in alcoholic liver disease.

• HFE mutations are not increased in frequency in alcoholic liver disease.

• Wilson's disease presents with low serum copper and ceruloplasmin, whereas alcoholic liver disease does not typically show these specific copper abnormalities.

6. INVESTIGATIONS & DIAGNOSIS

Currently, a formal diagnosis of Wilson's disease relies on a combination of clinical, biochemical, and molecular features. A scoring system (Leipzig) that weights and collates various signs and symptoms was

produced by an international expert group in 2001 and remains a valuable guide to diagnosis that is endorsed by the European Association for the Study of the Liver (EASL).

6.1 Laboratory Findings

- Laboratory findings that support the diagnosis of Wilson's disease include low levels of serum copper and serum ceruloplasmin, elevated hepatic transaminase levels, aminoaciduria, and hemolytic anemia.
- Increased urinary excretion of copper (>100 µg/24 h) is an easily performed and important diagnostic test for Wilson's disease.
- Acid-washed (copper-free) collection containers should be used.
- The penicillamine challenge is a variation using serial urine copper measurements in which 500 mg of penicillamine are administered orally after collecting a baseline 24-h urine.
- The penicillamine dose is repeated after 12 h, the midpoint of the second 24-h urine collection.
- A several-fold increase in copper excretion in the second collection suggests the diagnosis.
- Incorporation of radiolabeled 64Cu into serum ceruloplasmin, measured as the appearance of copper in the serum after an oral load, is a highly specific diagnostic test; patients with Wilson's disease incorporate very little 64Cu into ceruloplasmin.

6.2 Liver Biopsy

- Although invasive, percutaneous needle liver biopsy for measurement of hepatic copper remains a gold standard technique for biochemical diagnosis of Wilson's disease.
- Hepatic copper values >200 µg per gram of dry weight (normal 20–50 µg) are characteristic of Wilson's disease.
- Inductively coupled plasma mass spectrometry and atomic absorption spectrometry are preferred quantitative methods; histochemical staining for copper in liver biopsy specimens is considered less reliable.

6.3 Diagnostic Criteria Table

- Diagnosis relies on a combination of clinical, biochemical, and molecular features.
- Leipzig scoring system weights and collates various signs and symptoms.
- EASL endorses the Leipzig scoring system.

Table 1 Table 427-1 Main Diagnostic Features of Wilson's Disease

Clinical Signs and Symptoms	Biochemical Findings	Molecular Findings
Hepatic: Jaundice, Anorexia, Vomiting, Ascites and/or edema, Splenomegaly, Fatty liver, Cirrhotic liver, Hemolytic anemia, Renal Fanconi syndrome	Low serum copper, Low serum ceruloplasmin, Increased urinary copper excretion, Elevated liver enzymes, Hypoalbuminemia, Increased liver copper	Variants in ATP7B on both chromosomes
Neurologic: Dysarthria, Facial grimace (risus sardonicus), Drooling, Dysphagia, Dysgraphia, Dystonia, Tremor (wing-beating), Ataxia, Seizures (rare)	Increased liver enzymes, Hypoalbuminemia, Increased liver copper	Variants or polymorphisms in other genes (e.g., CAT, SOD2, MTHFR) may influence clinical expression of Wilson's disease in some individuals
Ocular: Kayser-Fleischer ring, Sunflower cataract (rare)	N/A	N/A

Clinical Signs and Symptoms	Biochemical Findings	Molecular Findings
Psychiatric: Decline in school performance, Personality change, Mood disorder, Schizophrenia	N/A	N/A

7. MANAGEMENT & TREATMENT

Prompt diagnosis in the presymptomatic or early symptomatic phase of the illness and lifelong treatment are needed to prevent premature mortality in affected individuals. Treatment potential of zinc salts to reduce gastrointestinal copper absorption in Wilson's disease was recognized in the early 1960s, eventually leading to FDA approval for this indication.

7.1 Pharmacologic Therapy

- Copper chelation therapy causes fading and eventual disappearance of corneal copper.
- Treatment with copper chelation often improves the renal disturbances.
- Drug regimens include:
- Penicillamine: 500 mg orally after collecting a baseline 24-h urine. The penicillamine dose is repeated after 12 h, the midpoint of the second 24-h urine collection. A several-fold increase in copper excretion in the second collection suggests the diagnosis.
- Triethylene tetramine: Second FDA-approved treatment for Wilson's disease.
- Zinc salts: Reduce gastrointestinal copper absorption.
- Tetrathiomolybdate: Forms a tripartite complex with copper and albumin, and a bacterial peptide, methanobactin, which traverses mitochondrial membranes. More recently proposed copper chelators with potential for treatment of Wilson's disease.

7.2 Surgical/Procedural Management

- Liver transplantation is indicated for end-stage liver disease or patients unresponsive to medical therapies.
- First liver transplants were performed for Wilson's disease in the early 1970s, with resultant correction of hepatic failure and crippling neurologic impairments in patients unresponsive to medical therapies.

7.3 Monitoring

- Treatment response criteria include fading and eventual disappearance of corneal copper.
- Treatment with copper chelation often improves the renal disturbances.
- Acid-washed (copper-free) collection containers should be used for urine copper measurements.

8. PROGNOSIS & COMPLICATIONS

Prompt diagnosis in the presymptomatic or early symptomatic phase of the illness and lifelong treatment are needed to prevent premature mortality in affected individuals. Hemolytic anemia due to the direct toxic effects of copper on red blood cell membranes is usually associated with release of massive quantities of hepatic copper into the circulation, a phenomenon that can be sudden and catastrophic.

8.1 Long-term Follow-up

- Lifelong treatment is needed to prevent premature mortality in affected individuals.

• Advances in the application of whole genome sequencing (and/or measurement of ATP7B peptides) from newborn dried blood spots may transform presymptomatic diagnosis for Wilson disease in the future.

8.2 Complications

• Hemolytic anemia: Direct toxic effects of copper on red blood cell membranes.

• Renal tubular dysfunction: Abnormal losses of amino acids, electrolytes, calcium, phosphorus, and glucose.

• Skeletal abnormalities: Osteoporosis, rickets, osteoarthritis.

• Neurologic impairment: Crippling neurologic impairments if untreated.

• Hepatic failure: End-stage liver disease.

9. SPECIAL CONSIDERATIONS

Wilson's disease should be formally excluded in all teenagers and young adults with new-onset psychiatric signs. Wilson's disease may be mistaken for Parkinson disease or other movement disorders. Wilson's disease is an autosomal recessive inherited disorder of copper transport that primarily impacts the liver and brain. This reflects the critical need for homeostatic mechanisms to properly utilize this trace metal, both systemically and in the central nervous system.

9.1 Age of Presentation

• Nearly all individuals who present with liver disease are <30 years of age.

• Those presenting with neurologic or psychiatric signs may range in age from the first to the fifth decade.

• Typically, patients presenting with psychiatric signs are in their late teens or early twenties, a period during which substance abuse is also a diagnostic consideration.

9.2 Newborn Screening

• Advances in the application of whole genome sequencing (and/or measurement of ATP7B peptides) from newborn dried blood spots may transform presymptomatic diagnosis for Wilson disease in the future.

10. KEY PEARLS & CLINICAL TRAPS

Wilson's disease is an autosomal recessive inherited disorder of copper transport that primarily impacts the liver and brain. Wilson's disease should be formally excluded in all teenagers and young adults with new-onset psychiatric signs. Wilson's disease may be mistakenly diagnosed as Parkinson disease or other movement disorders. Wilson's disease can properly be classified as a movement disorder. The neurologic signs and symptoms reflect the predilection for basal ganglia (e.g., caudate, putamen) involvement in the brains of affected persons.

10.1 Diagnostic Clues

• Kayser-Fleischer ring: Pathognomonic sign, golden to greenish-brown band in the peripheral cornea.

• Hepatic copper values >200 µg per gram of dry weight (normal 20–50 µg) are characteristic of Wilson's disease.

• Increased urinary excretion of copper (>100 µg/24 h) is an easily performed and important diagnostic test for Wilson's disease.

• Low levels of serum copper and serum ceruloplasmin support the diagnosis.

• Hemolytic anemia is associated with release of massive quantities of hepatic copper into the circulation.

10.2 Clinical Traps

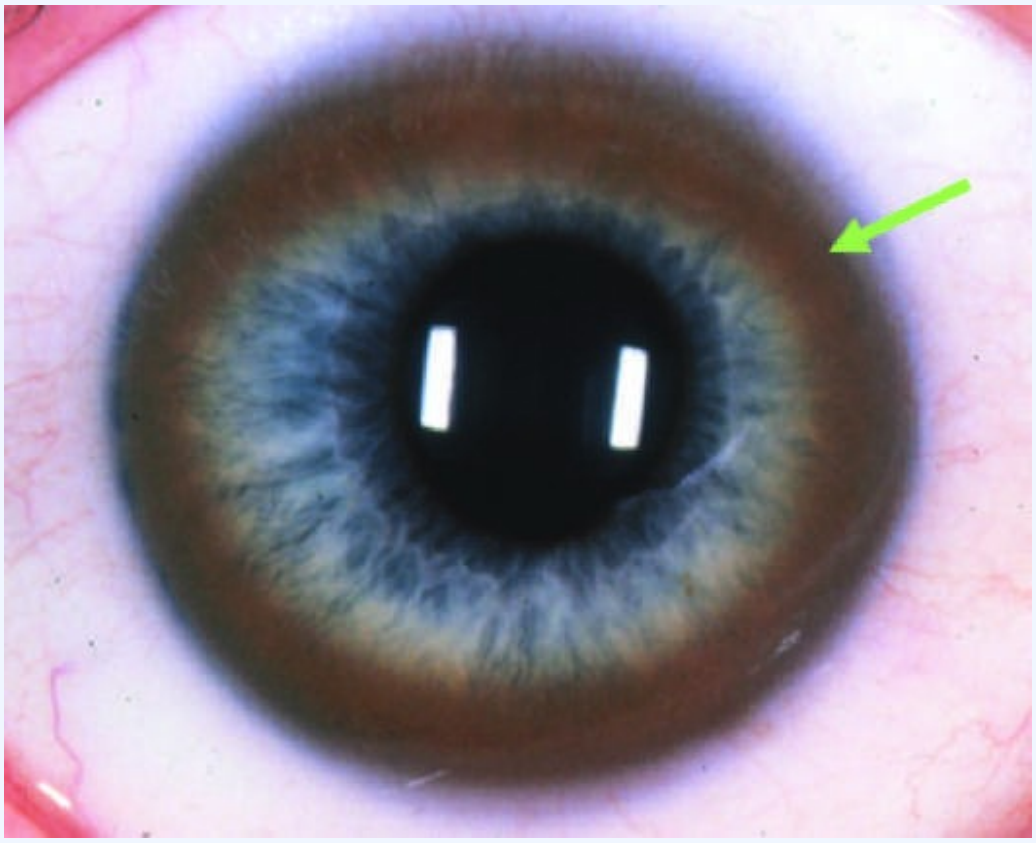
• Wilson's disease should be formally excluded in all teenagers and young adults with new-onset psychiatric signs.

• Wilson's disease may be mistakenly diagnosed as Parkinson disease or other movement disorders.

• Viral hepatitis and cirrhosis are often initial diagnostic considerations in individuals who, in fact, have Wilson's disease.

• HFE mutations are not increased in frequency in alcoholic liver disease, but alcohol does reduce hepcidin expression, which accounts for increased iron absorption and hepatic iron sometimes seen in alcoholic liver disease.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



Harrison's 22e · Figure 1

FIGURE 427-1 Kayser-Fleischer ring in Wilson's disease, representing copper deposition in Descemet membrane of the cornea. (Image courtesy of Tjaard U. Hoogenraad MD, PhD, Department of Neurology, University Medical Centre Utrecht, Utrecht, The Netherlands.) — Figure 427-1 Kayser-Fleischer ring in Wilson's disease, representing copper deposition in Descemet membrane of the cornea. The ring appears as a golden to greenish-brown band in the peripheral cornea, first as a superior crescent, then developing inferiorly, and ultimately becoming circumferential.