Wilson disease: Clinical manifestations, diagnosis, and natural history

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INTRODUCTION

Wilson disease (also referred to as hepatolenticular degeneration) is a genetic disorder of copper metabolism with an autosomal recessive pattern of inheritance that leads to impaired function of the intracellular copper transporter ATP7B. Reduced biliary excretion of copper results in its accumulation in the liver and other tissues (eg, brain, cornea). Most patients have liver involvement that may range from asymptomatic elevations in liver biochemistries (eg, serum aminotransferases, bilirubin) to cirrhosis or acute liver failure. Some patients develop symptoms related to neurologic involvement.

This topic will discuss the clinical manifestations, diagnosis, and natural history of Wilson disease. Other aspects of Wilson disease are discussed separately:

- Epidemiology and pathogenesis – (See "Wilson disease: Epidemiology and pathogenesis".)
- Interpretation of genetic testing for *ATP7B* (Wilson disease gene) – (See "Gene test interpretation: *ATP7B* (Wilson disease gene)".)
- Management – (See "Wilson disease: Treatment and prognosis".)

CLINICAL FEATURES

Patterns of clinical presentation — Wilson disease has a variety of clinical phenotypes; thus, it may be included in the differential diagnosis for patients with abnormal liver biochemical tests, chronic hepatitis, cirrhosis, or acute liver failure [1,2]. (See "Approach to the patient with abnormal liver biochemical and function tests".)

The spectrum of presentation also includes patients with isolated neuropsychiatric symptoms and asymptomatic patients. Some patients have a combination of hepatic and extrahepatic symptoms. A non-immune (Coombs-negative) hemolysis is common in patients with acute liver failure due to Wilson disease, but it may also occur in the absence of acute liver failure.

The reported rates of organ-specific manifestations at the time of presentation vary widely [1,3-8]:

- Liver disease: 18 to 84 percent of patients
- Neurologic symptoms: 18 to 73 percent of patients
- Psychiatric symptoms: 10 to 100 percent of patients

The wide variability in these estimates may be attributable to lead-time bias with respect to the age at which a patient is seen, as well as ascertainment bias based on the clinical specialty to which the patient was referred (eg, neurologists are more likely to see patients with neurologic symptoms, whereas pediatricians are less likely). (See 'Age at symptom onset' below.)

Regardless of whether clinical manifestations are initially present, patients often develop manifestations of organ-specific involvement as the disease progresses (eg, patients who present with liver disease may subsequently develop neurologic or psychiatric symptoms). Conversely, liver failure may develop in patients who presented initially with neurologic or psychiatric symptoms.

Age at symptom onset — Most patients with Wilson disease develop symptoms between the ages of 3 and 55 years, although the disorder has been diagnosed in patients under the age of three years and in patients in their eighth decade [9-11]. In a study of 143 pediatric patients with Wilson disease, 21 patients (15 percent) presented with symptoms or abnormal liver biochemistries before the age of five years [10].

Most symptomatic pediatric patients (ie, <18 years of age) present with liver disease alone, whereas symptomatic adults have liver disease with or without neurologic symptoms. However, individuals who are diagnosed through family screening because of an affected first-degree relative are often asymptomatic, regardless of age.

The mechanisms for copper excretion are not well developed in newborns and begin to function more efficiently within the first year of life. For patients with Wilson disease, a critical *ATP7B*-dependent copper excretory pathway fails to develop or is dysfunctional, and copper accumulation that begins at birth continues throughout life, gradually producing clinical disease [12]. In most patients, liver disease progresses silently, often until adolescence and beyond, when acute liver failure or complications of cirrhosis may develop. In some patients, neurologic or psychiatric manifestations precede overt liver disease.

The variability in the age of onset of Wilson disease probably reflects differences in mutations and penetrance, extragenic factors, and environmental influences including diet [13]. (See "Wilson disease: Epidemiology and pathogenesis".)

Manifestations of copper accumulation

Liver disease — The liver is a major site of copper accumulation in Wilson disease. Clinical presentation of liver involvement ranges from asymptomatic elevations in liver biochemistries (often with steatosis) to acute liver injury/failure (often with an associated non-immune hemolytic anemia) or to chronic hepatitis and cirrhosis. Regardless of presenting symptoms, some degree of liver disease, even if only histologic change, is usually present at the time of diagnosis [14]. Approximately 5 to 25 percent of patients with liver involvement do not report any symptoms.

The clinical features vary with the degree of liver damage [1,15]. Patients with copper accumulation in the liver may present with (see "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'):

- Abdominal pain (acute hepatitis, acute liver failure)
- Jaundice (acute hepatitis, acute liver failure with hemolytic anemia, cirrhosis)
- Hepatomegaly (acute and chronic hepatitis, acute liver failure)
- Splenomegaly (cirrhosis with portal hypertension)
- Ascites (cirrhosis with portal hypertension)
- Upper gastrointestinal bleeding from varices or portal hypertensive gastropathy
- Peripheral stigmata of chronic liver disease (cirrhosis)
- Mental status changes due to hepatic encephalopathy (acute liver failure, cirrhosis)

Laboratory test findings may include:

- Low level of serum ceruloplasmin (may be seen with all forms of liver involvement, although not as consistently with acute liver failure)

- Elevated aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST])
- Low alkaline phosphatase
- Thrombocytopenia
- Coagulopathy
- Non-immune hemolytic anemia

Abdominal imaging may show:

- Liver steatosis
- Hepatomegaly
- A small, nodular liver
- Splenomegaly
- Ascites
- Varices and/or patent umbilical vein
- Portosystemic shunt (ie, splenorenal)

Liver histologic findings may include fatty infiltration within hepatocytes, glycogen inclusions within nuclei, and portal fibrosis, especially earlier in the course of the disease (picture 1).

Acute liver injury/failure — Acute liver injury in patients with Wilson disease manifests initially as abdominal pain and jaundice that progresses to liver failure. Most patients have underlying advanced fibrosis or cirrhosis; thus, the condition may be referred to as acute on chronic liver failure (ACLF) [16]. In contrast, acute liver failure refers to the rapid (typically in less than 8 to 12 weeks) development of severe acute liver injury with impaired synthetic function with coagulopathy and encephalopathy in an individual who previously had a normal liver. (See "Acute liver failure in children: Etiology and evaluation" and "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

Features of ACLF related to Wilson disease include [17,18]:

- Non-immune (Coombs-negative) hemolytic anemia results from the effects of excess copper ions on the red blood cell membrane in the circulation due to hepatic copper release following cellular necrosis [19,20]. (See "Non-immune (Coombs-negative) hemolytic anemias in adults".).

- Coagulopathy unresponsive to parenteral administration of Vitamin K.

- Elevated aminotransferases (typically <2000 international units/L). The ratio of the AST to ALT is often >2.

- Normal or markedly low serum alkaline phosphatase (typically <40 international units/L). The ratio of the alkaline phosphatase (international unit/L) to total bilirubin (mg/dL) is typically <4.
- Rapidly progressive kidney failure.
- Low uric acid levels.
- Female to male ratio of 2:1 to 4:1 [21].

Ceruloplasmin levels are less reliable for diagnosing ACLF due to Wilson disease because ceruloplasmin is an acute phase reactant, which may elevate levels [16]. Alternatively, ceruloplasmin levels can be depressed due to severe liver synthetic dysfunction.

Chronic liver disease and cirrhosis — Patients with chronic hepatitis due to Wilson disease are often asymptomatic from their liver disease. It has been estimated that 35 to 45 percent of patients have cirrhosis at the time of diagnosis of Wilson disease [22-24]. Such patients are typically diagnosed through family screening, after presenting with neurologic or psychiatric manifestations, or during an evaluation for abnormal liver biochemical tests or imaging. Serum aminotransferases are usually mildly to moderately elevated (ie, <5 times the upper limit of normal) in asymptomatic patients with Wilson disease. AST is usually higher than ALT. Wilson disease often results in liver steatosis and may be diagnosed in a patient being evaluated for steatotic liver disease [15].

Most patients with chronic liver disease have low serum ceruloplasmin, but only 50 percent have Kayser-Fleischer (KF) rings. On liver biopsy, nearly all patients have a hepatic copper concentration >250 mcg/g dry weight liver, but few patients have levels as low as 75 mcg/g dry weight liver, with normal being <40 mcg/g dry weight liver [23].

As the disease progresses, patients may develop cirrhosis with or without complications such as ascites or variceal bleeding. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Of note, the magnitude of aminotransferase elevation correlates poorly with the extent of histologic injury [25,26].

Neurologic involvement — Neurologic manifestations of Wilson disease vary widely. Nearly all patients with Wilson disease with neurologic manifestations have KF rings. Neurologic symptoms may be subtle or may be rapidly progressive, leading to severe disability over the course of months [27]. In patients with known cirrhosis, neurologic manifestations may be mistaken for hepatic encephalopathy.

Most patients with neurologic involvement have at least one of the following features [1,28-30]:

- **Dysarthria** – Dysarthria is common and has been reported in up to 97 percent of patients with neurologic manifestations. The type of dysarthria varies and includes ataxic dysarthria (irregular word spacing and volume) and athetoid, hypophonic, or spastic speech.

- **Cerebellar ataxia/abnormal gait** – Cerebellar ataxia is generally not seen as the sole neurologic manifestation of Wilson disease, but it has been reported in 30 to 75 percent of patients with Wilson disease [1]. The ataxia is typically not clinically relevant, and frank limb ataxia is uncommon.

  Patients with cerebellar ataxia have difficulty changing voluntary force levels abruptly, with impaired acceleration and braking [31]. This may lead to overshoot in point-to-point movements (dysmetria); breakdown of normal coordination of joint rotations, with trajectory abnormalities (dyssynergia in multi-joint movements); and breakdown in the rhythm of repetitive, alternating single movements, such as finger tapping (dysrhythmia) [32].

  Dysfunction in the vermis or paleocerebellum results in truncal and gait ataxia. (See "Causes and evaluation of neurologic gait disorders in older adults".)

- **Dystonia** – Reported rates of dystonia in patients with Wilson disease have ranged from 38 to 69 percent. Dystonia may range in severity from mild to debilitating, and it often worsens with disease progression [1]. Dystonia may be focal, segmental, multifocal, or generalized. While it can occur unilaterally, it may eventually become bilateral or generalized. In some patients with severe dystonia, contractures may develop and may only be corrected with surgical tendon lengthening. (See "Etiology, clinical features, and diagnostic evaluation of dystonia".)

  Focal manifestations of dystonia include blepharospasm, cervical dystonia (torticollis), writer's cramp, and a dystonic facial expression in which the patient appears to have an exaggerated smile (risus sardonicus). In addition, focal dystonia may involve the vocal cords (dysphonia), muscles of articulation (dysarthria), or swallowing muscles (dysphagia).

- **Tremor** – Tremors in Wilson disease have been reported in up to 55 percent of patients. Tremors may occur at rest or with action and may have multiple position and task-dependent characteristics [1]. Specific types of tremor include:

- Postural tremor that occurs when the patient assumes a particular position. The classic tremor associated with Wilson disease is a wing-beating tremor, although it is not the most common type of tremor [1]. The tremor is a low-frequency, high-amplitude tremor that is most prominent when the patient's arms are held outstretched laterally or with the arms extended in front of the patient with the palms facing downward and the elbows flexed. The tremor increases in amplitude with increased duration of posture holding. The name comes from the fact that the movement of the patient's arms may resemble a bird's flapping wings.

- A tremor that resembles essential tremor (variable amplitude and frequency, with arm and sometimes head and leg involvement). However, unlike essential tremor, the tremor in Wilson disease often persists in its asymmetry and may not involve the voice. (See "Overview of tremor", section on 'Essential tremor'.)

- Intention (kinetic) tremor (low amplitude, medium-to-high frequency). These intention tremors are seen most often in a distal upper extremity and typically increase in severity as the patient's hand moves closer to its target. (See "Overview of tremor", section on 'Cerebellar tremor'.)

- Unilateral rest tremor. A unilateral rest tremor may be present and is typically accompanied by postural and intention tremors [4].

- **Parkinsonism** – Parkinsonian movement disorder has been reported in 12 to 58 percent of patients. Specific features include bradykinesia, cogwheel rigidity, and postural instability. Parkinsonism is rarely an isolated clinical feature and is typically accompanied by other neurologic deficits. [1].

Less common neurologic manifestations include [28-30]:

- **Chorea/athetosis** – Chorea is characterized by rapid and unpredictable contractions affecting mostly distal limbs, but it can also affect the face and trunk. The movements are involuntary and non-patterned with variable speed, timing, and direction, flowing from one body part to another. In less severe cases, this can result in an appearance of fidgeting. The unpredictable nature of chorea is a feature that distinguishes it from tremor and dystonia [33]. When it is severe and involves proximal muscle(s), choreic movements may result in violent, uncontrolled flailing movements of the extremities (ballism). Athetosis refers to slower writhing movements with a sinuous quality. The term choreoathetosis is used when typical choreic movements coexist with athetosis. (See "Overview of chorea".)

Chorea is seen more often in younger patients (≤16 years of age) and typically occurs in combination with other neurologic symptoms [1,34].

- **Cognitive impairment** – Cognitive impairment in Wilson disease may be manifested as a frontal syndrome or subcortical dementia, with some patients having features of both [1]. In patients with cognitive impairment, the findings can be subtle and may only be recognized retrospectively. For patients with new onset cognitive changes, it is important to exclude hepatic encephalopathy. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

  Patients with a frontal syndrome may demonstrate impulsivity, promiscuity, impaired judgement, apathy, executive dysfunction (eg, poor planning and decision-making), decreased attention, and emotional lability. When severe, patients may have pseudobulbar features (sudden outbursts of inappropriate laughter or tearfulness). (See "Frontotemporal dementia: Clinical features and diagnosis", section on 'Behavioral variant FTD'.)

  Findings in subcortical dementia include slowed thinking, memory loss, and executive dysfunction. However, patients with subcortical dementia lack cortical signs such as aphasia, apraxia, or agnosia.

- **Seizures** – Seizures have been reported infrequently during initial chelation therapy or later in the course of disease [35,36].

- **Dysautonomia** – Dysautonomia (eg, abnormal cardiac responses to the Valsalva maneuver) has been reported in Wilson disease usually in combination with other neurologic symptoms [37].

- **Other neurologic manifestations** – Other reported manifestations include hyperreflexia/hyperkinetic movements, myoclonus, and drooling.

Magnetic resonance imaging (MRI) of the brain may reveal structural abnormalities in the basal ganglia or striatal and thalamic atrophy [38-40]. Common findings in the basal ganglia include increased density on T2-weighted MRI images. Other findings include T2 hyperintensities in the tectal-plate and central pons. Simultaneous involvement of the basal ganglia, thalamus, and brainstem is highly suggestive of Wilson disease. Midbrain involvement sometimes appears as the "face of the giant panda," with the pontine changes resembling the face of a cub. This constitutes the characteristic "double panda sign."

Psychiatric symptoms — Psychiatric symptoms are common and may occur alone or in combination with liver and/or neurologic manifestations. Symptoms are generally nonspecific and include mood disorders (depression or bipolar spectrum), psychosis, sleep disturbance, and cognitive changes [17]. Less common psychiatric manifestations of Wilson disease are personality changes (which may be subtle), irritability, impulsivity, labile mood, and declining academic/work performance [41-43].

Ocular involvement — Kayser-Fleischer (KF) rings are golden-brownish rings that result from fine, pigmented, granular deposits of copper in the periphery of the cornea (picture 2). KF rings are a characteristic feature of Wilson disease found in nearly all patients with neurologic involvement and in approximately 50 percent of patients with liver disease. KF rings are usually detected by slit-lamp examination or by anterior segment optical tomography [44-47]. Optical tomography can also quantify the ring size [48]. KF rings dissipate over time with chelation or zinc therapy or following liver transplantation. (See "Slit lamp examination".)

Sunflower cataracts are another ocular manifestation of Wilson disease and occur when copper deposits accumulate in the lens. These are generally detected by slit-lamp examination [49].

Other organs — Less common manifestations of Wilson disease related to copper deposition in other organs are [44]:

- Kidney – Kidney abnormalities include Fanconi syndrome, in which proximal tubular dysfunction leads to glucosuria, aminoaciduria, hypouricemia (related to an increase in uric acid secretion), proximal renal tubular acidosis, and distal renal tubular acidosis that results in nephrolithiasis. (See "Etiology and diagnosis of distal (type 1) and proximal (type 2) renal tubular acidosis", section on 'Proximal (type 2) RTA' and "Nephrolithiasis in renal tubular acidosis".)

- Rheumatologic – Rheumatologic manifestations include myopathy of the proximal limb muscles and arthropathy with premature arthritis and occasionally chondrocalcinosis, most commonly in the knee.

- Cardiac – Cardiomyopathy.

- Endocrine organs – Hypoparathyroidism; gigantism; female infertility and/or recurrent pregnancy loss; male sexual dysfunction.

- Dermatologic – Blue lunulae (lunulae ceruleae), acanthosis nigricans, and pretibial hyperpigmentation.

Hemolysis — Non-immune (Coombs-negative) hemolytic anemia may rarely be the initial presentation of Wilson disease and is not uniformly associated with acute liver failure [50,51]. In a series of 283 patients with Wilson disease, hemolytic anemia was the sole presenting feature in three patients (1 percent), but it was present in 19 of 77 patients (28 percent) who had jaundice at presentation [50]. Hemolytic anemia may occur as a single acute episode, or it may be low-grade, episodic, or chronic.

Patients reporting a history of jaundice prior to the diagnosis may have had previously unrecognized hemolysis [52]. If acute hepatitis and hemolysis due to Wilson disease develop during pregnancy, it may be mistaken for HELLP syndrome. In patients with acute liver failure, hemoglobin <10 g/dL has been associated with a 94 percent sensitivity but only 74 percent specificity for a diagnosis of Wilson disease [16]. (See "Overview of hemolytic anemias in children" and "Diagnosis of hemolytic anemia in adults" and "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)

DIAGNOSTIC EVALUATION

When to suspect Wilson disease — Wilson disease may be suspected in patients with any of the following:

- Unexplained liver biochemical abnormalities (eg, elevated aminotransferases), especially if they are accompanied by neurologic or psychiatric symptoms. (See 'Liver disease' above.)
- Low ceruloplasmin (<20 mg/dL [<200 mg/L], with higher suspicion if ceruloplasmin is <14 mg/dL [<140 mg/L]).
- A first-degree relative with Wilson disease.
- Other clinical feature suggestive of copper overload:
  - Chronic liver disease or cirrhosis of uncertain etiology (eg, patients with autoimmune hepatitis who do not respond to therapy, patients with liver steatosis in the absence of metabolic risk factors). (See "Overview of autoimmune hepatitis" and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)
  - Acute liver failure in combination with other features of Wilson disease (eg, non-immune hemolytic anemia). (See 'Acute liver injury/failure' above.)
  - Unexplained neurologic symptoms (eg, parkinsonian-like rest tremor, rigidity, gait abnormality, slurring of speech, facial grimacing [risus sardonicus]).

- Unexplained psychiatric symptoms, ranging from changes in personality or work/school performance to depression or psychosis. (See 'Neurologic involvement' above and 'Psychiatric symptoms' above.)

Symptomatic patients

Initial testing — For symptomatic patients, we use a stepwise approach to establish the diagnosis of Wilson disease. Testing begins with an ocular examination for Kayser-Fleischer (KF) rings and laboratory studies. If initial testing is inconclusive, we obtain liver biopsy and/or genetic testing. (See 'When to suspect Wilson disease' above and 'Subsequent testing' below.)

Initial testing includes (table 1):

- An ocular slit-lamp examination or anterior segment optical tomography
- 24-hour urinary copper excretion
- Serum ceruloplasmin

We also measure serum aminotransferases, complete blood count, and serum copper concentration during the initial laboratory evaluation.

We obtain the following in selected patients:

- For patients with acute liver injury/failure, we evaluate for non-immune hemolytic anemia (table 2). The diagnosis of hemolytic anemia is discussed separately. (See "Diagnosis of hemolytic anemia in adults".)
- For patients with neurologic symptoms, we obtain brain imaging, usually with MRI without contrast enhancement.

Liver biopsy is not always necessary because the diagnosis can be established in some patients with noninvasive testing and ocular examination. (See 'Patients with KF rings' below and 'Patients without KF rings' below.)

We also use a standardized scoring system as part of the assessment (table 3). (See 'Diagnostic scoring system' below.)

Patients with KF rings — For symptomatic patients with KF rings, the diagnosis of Wilson disease is established if either of following criteria are met (algorithm 1) (see 'Manifestations of copper accumulation' above):

- 24-hour urinary copper excretion >40 mcg/24 hours (0.64 micromol/24 hours) in addition to ceruloplasmin <20 mg/dL (200 mg/L), or

- 24-hour urinary copper excretion >100 mcg/24 hours (1.6 micromol/24 hours), regardless of ceruloplasmin level

For patients who do not meet either of these criteria, we obtain a liver biopsy to determine the hepatic copper concentration and/or molecular genetic testing for *ATP7B* mutations. For patients with discordant findings (eg, symptomatic patient with KF ring, elevated urinary copper excretion but normal ceruloplasmin), we typically obtain genetic testing also because normal ceruloplasmin is uncommon in patients with Wilson disease. (See 'Subsequent testing' below.)

Patients without KF rings — For symptomatic patients without KF rings, the diagnosis of Wilson disease is established if the following criteria are met (algorithm 2) (see 'Manifestations of copper accumulation' above):

- 24-hour urinary copper excretion >100 mcg/24 hours (1.6 micromol/24 hours) in addition to ceruloplasmin <10 mg/dL (<100 mg/L)

For patients with either ceruloplasmin <10 mg/dL only or elevated 24-hour urinary copper excretion (ie, >40 mcg/24 hours [0.64 micromol/24 hours]) only, we obtain a liver biopsy to determine the hepatic copper concentration and/or genetic testing for *ATP7B* mutations. (See 'Subsequent testing' below.)

For symptomatic patients (eg, elevated aminotransferases, hepatomegaly) with ceruloplasmin ≥10 mg/dL and 24-hour urinary copper excretion ≤40 mcg/24 hours (0.64 micromol/24 hours), the diagnosis of Wilson disease is excluded.

Subsequent testing

Liver biopsy — For patients with inconclusive initial testing who undergo a liver biopsy, we determine hepatic copper concentration [23,53] (see 'Initial testing' above):

- A diagnosis of Wilson disease is established if the hepatic copper concentration is >250 mcg/g dry weight (4 micromol/g dry weight).

- A diagnosis of Wilson disease is excluded if the hepatic copper concentration is <50 mcg/g dry weight (0.8 micromol/g dry weight).

If the hepatic copper concentration is between 50 and 250 mcg/g dry weight liver, we obtain molecular genetic testing for *ATP7B* mutations. In addition, we obtain genetic testing if we

suspect sampling variation leading to a falsely normal hepatic copper concentration. (See 'Genetic testing' below.)

Liver biopsies in patients suspected of having Wilson disease should include one needle core specimen for histology and one for copper quantitation that are both at least 1 cm in length. The specimen for copper quantitation should be placed in a dry, copper-free container [27]. Specimen collection methods for copper quantitation, such as freezing or vacuum drying the specimen, prevent tissue destruction and provide accurate specimen weight. (See "Approach to liver biopsy".)

In addition to being widely available, liver biopsy informs disease staging and excludes other causes of liver disease.

Genetic testing — We use genetic testing when the diagnosis remains uncertain despite initial testing, when liver biopsy is not possible or inconclusive (ie, hepatic copper concentration between 50 and 250 mcg/g dry weight liver), and for evaluating siblings when the mutations in the proband are known. (See 'Initial testing' above.)

We refer patients who undergo genetic testing to a genetic counselor. (See "Genetic testing".)

Biallelic, pathogenic (disease-causing) variants affecting both ATP7B alleles are required to develop Wilson disease. The genetics of Wilson disease and interpretation of genetic testing are discussed in detail separately. (See "Wilson disease: Epidemiology and pathogenesis", section on 'Genetic defect in Wilson disease' and "Gene test interpretation: *ATP7B* (Wilson disease gene)".)

A database of mutations in *ATP7B* (the gene mutated in Wilson disease) is available online [54].

Diagnostic scoring system — A scoring system for assessing the certainty of the diagnosis was developed at an international meeting in Leipzig, Germany [55]. The scoring system includes biochemical testing (eg, ceruloplasmin, urinary copper excretion), clinical manifestations (KF rings and neurologic symptoms), and molecular testing for *ATP7B* mutations (table 3) [27]. If the score is ≥4, Wilson disease is highly likely; if it is 3, the diagnosis is probable, but additional testing is needed (eg, obtaining a liver biopsy if not already done); if it is ≤2, Wilson disease is unlikely.

Asymptomatic first-degree relatives — All first-degree relatives of patients diagnosed with Wilson disease require evaluation, and we screen siblings with *ATP7B* genetic testing based on the proband (algorithm 3). Because direct mutation analysis is available, targeted testing of

siblings is specific and generally cost-effective. Interpretation of genetic testing for *ATP7B* is discussed separately. (See "Gene test interpretation: *ATP7B* (Wilson disease gene)".)

If genetic testing is not available, we evaluate siblings with clinical and laboratory testing similar to the evaluation for patients with clinical features but no family history of Wilson disease. (See 'Initial testing' above.)

For asymptomatic siblings diagnosed by genetic screening, we also assess for copper overload by measuring 24-hour urinary copper excretion or hepatic copper concentration because individuals with two disease-causing mutations do not always have abnormal copper metabolism.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Wilson disease includes conditions associated with chronic liver inflammation or acute liver injury, in addition to conditions with similar neuropsychiatric features:

Other causes of liver disease — Evaluation for other causes of liver disease is informed by patient presentation:

- Chronic hepatitis with or without cirrhosis – Similar to Wilson disease, individuals with other causes of chronic liver disease may have elevated aminotransferases but do not have low ceruloplasmin. Such disorders include viral hepatitis, alcohol use disorder, autoimmune hepatitis, drug-induced liver injury, hereditary hemochromatosis, and alpha-1 antitrypsin deficiency. In patients with Wilson disease, the serum aminotransferases are usually mildly to moderately elevated (ie, <5 times the upper limit of normal), and the aspartate aminotransferase (AST) concentration is usually higher than the alanine aminotransferase (ALT) concentration. (See "Approach to the patient with abnormal liver biochemical and function tests".)

  Similarly, in patients presenting with cirrhosis, we evaluate patients for other causes of chronic liver disease, such as viral hepatitis. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis".)

- Acute liver injury – The differential diagnosis of acute liver injury that progresses to liver failure is broad and includes toxins, viral hepatitis, ischemia, and autoimmune hepatitis. Among patients with acute liver failure due to Wilson disease, the serum aminotransferases are typically less than 2000 international units/L with an AST/ALT ratio

of >2 [16]. In addition, the alkaline phosphatase level is typically normal or below the normal range, with an alkaline phosphatase (international unit/L) to total bilirubin (mg/dL) ratio of <4. Finally, patients with acute liver failure due to Wilson disease typically develop a non-immune hemolytic anemia and may have a low uric acid level. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis" and "Acute liver failure in children: Etiology and evaluation".)

Other causes of neurologic symptoms — The neurologic manifestations of Wilson disease vary widely and can mimic other neurologic disorders, especially any type of movement disorder. The differential diagnosis includes essential tremor, young-onset Parkinson disease, and generalized dystonia. The presence of KF rings, seen in nearly all patients with neurologic Wilson disease, help differentiate Wilson disease from other disorders. In addition, patterns of injury on brain imaging (eg, MRI) may support the diagnosis of Wilson disease [56]. (See "Overview of tremor" and "Etiology, clinical features, and diagnostic evaluation of dystonia" and "Bradykinetic movement disorders in children" and "Neuroacanthocytosis".)

In addition, neurologic symptoms may be related to hepatic encephalopathy that occurs in patients with portosystemic shunting, decompensated cirrhosis, or acute liver failure. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis".)

Other causes of psychiatric symptoms — The differential diagnosis for the psychiatric manifestations of Wilson disease includes depression, bipolar disorder, schizophrenia, dementia, and substance use disorder. As with the neurologic manifestations, KF rings can help differentiate patients with Wilson disease from these other disorders. (See "Unipolar depression in adults: Assessment and diagnosis" and "Bipolar disorder in adults: Epidemiology and pathogenesis" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)

DISEASE COURSE

Progressive multisystem disease — Patients with disease limited to the liver and who respond to drug therapy are unlikely to develop neurologic symptoms [57]. However, for patients with untreated Wilson disease, copper accumulation in the liver eventually leads to cirrhosis and complications of portal hypertension (eg, ascites, variceal bleeding).

Among untreated patients with neurologic involvement, the neurologic symptoms may progress until the patient becomes severely dystonic, akinetic, and mute. Progression is usually gradual, but sudden deterioration may also occur. Mortality is usually related to liver disease

(decompensated cirrhosis or acute liver failure), although some patients succumb to complications from progressive neurologic disease. (See 'Survival' below.)

Survival — For patients who achieve copper detoxification before developing cirrhosis and who maintain normal copper balance, overall survival is not significantly different compared with the general population [3,58-61].

Although life expectancy for untreated patients with Wilson disease is uncertain, lack of pharmacologic therapy and/or liver transplantation typically results in progressive symptoms, liver failure with complications of portal hypertension, and death. In addition, the estimated mortality rate for patients with Wilson disease complicated by acute liver failure who do not receive liver transplantation is 95 percent, with death usually occurring in days to weeks [62]. However, liver transplantation cures Wilson disease, and long-term outcomes following liver transplantation are generally excellent [63]. (See "Wilson disease: Treatment and prognosis".)

Risk of liver cancer — For patients with cirrhosis related to Wilson disease, we typically screen for hepatocellular carcinoma (HCC) using transabdominal ultrasound, and this approach is consistent with society guidelines [17,64-66]. Indications for surveillance, routine surveillance intervals, and management of imaging results are discussed separately. (See "Surveillance for hepatocellular carcinoma in adults", section on 'Patients with cirrhosis'.)

Whether the risk of HCC in patients with Wilson disease and cirrhosis meets the threshold for cost effective HCC surveillance is uncertain because data are limited [64-67]. Cost-effectiveness models suggested that in patients with cirrhosis, surveillance becomes cost-effective once the annual incidence of HCC exceeds 1.5 percent [68]. In a study including 130 patients with Wilson disease and cirrhosis who were followed for a mean of 15 years, two patients developed HCC (1.5 percent) [65]. The estimated annual HCC risk in patients with cirrhosis was 0.14 percent. In a single center study including 71 patients with Wilson disease who were followed for a mean of 92 months, five patients (7 percent) developed HCC [67].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Inherited liver disease".)

SUMMARY AND RECOMMENDATIONS

- **Background** – Wilson disease (also referred to as hepatolenticular degeneration) is a genetic disorder of copper metabolism that leads to impaired function of the intracellular copper transporter ATP7B. Reduced biliary excretion of copper results in its accumulation in the liver and other tissues (eg, brain, cornea). Most patients have liver involvement that may range from asymptomatic abnormalities in liver biochemistries (eg, elevated serum aminotransferases) to cirrhosis to acute liver injury/failure. (See 'Introduction' above.)

- **Clinical features** – Most patients with Wilson disease are diagnosed between the ages of 3 and 55 years, although it has been diagnosed in younger patients and in patients in their eighth decade of life. (See 'Age at symptom onset' above.)

  The spectrum of presentation ranges from asymptomatic patients to those with symptoms related to liver, neurologic and/or psychiatric involvement:

  - **Liver disease** – At the time of diagnosis, most patients have some degree of liver disease that ranges from asymptomatic abnormalities in liver biochemistries to cirrhosis or acute liver injury. (See 'Liver disease' above.)

  - **Neurologic symptoms** – Common manifestations of neurologic involvement include dysarthria and movement disorders (eg, gait abnormalities, dystonia, tremor, parkinsonism). (See 'Neurologic involvement' above.)

  - **Psychiatric symptoms** – Psychiatric symptoms are generally nonspecific and include mood disorders, psychosis, sleep disturbance, and cognitive changes. (See 'Psychiatric symptoms' above.)

  - **Other manifestations** – Other clinical and laboratory manifestations include Kayser-Fleischer rings (picture 2) and non-immune (Coombs-negative) hemolytic anemia. (See 'Ocular involvement' above and 'Hemolysis' above.)

- **When to suspect Wilson disease** – Wilson disease may be suspected in patients with any of the following (see 'When to suspect Wilson disease' above):

  - Unexplained liver biochemical abnormalities (eg, elevated aminotransferases), especially if they are accompanied by neurologic or psychiatric symptoms.

  - Low ceruloplasmin (<20 mg/dL [<200 mg/L] with higher suspicion if ceruloplasmin is <14 mg/dL [<140 mg/L]).

  - A first-degree relative with Wilson disease.

- Other feature suggestive of copper overload (eg, chronic liver disease of uncertain etiology, unexplained neurologic symptoms such as dysarthria, gait abnormality).

- **Diagnostic evaluation** – Initial diagnostic testing includes an ocular slit-lamp examination (or anterior segment optical tomography), 24-hour urinary copper excretion, and serum ceruloplasmin (table 1). Liver biopsy is not always necessary because the diagnosis can be established in some patients with noninvasive testing and ocular examination (algorithm 1 and algorithm 2). (See 'Diagnostic evaluation' above.)

  For patients in whom the diagnosis remains suspected but not established based on initial testing, additional studies include liver biopsy to assess hepatic copper concentration and/or molecular genetic testing to evaluate for pathogenic (disease-causing) variants affecting both ATP7B alleles.

  We also use a standardized scoring system as part of the assessment (table 3).

- **Disease course** – The prognosis for patients who achieve copper detoxification before developing cirrhosis and who maintain normal copper balance is excellent. (See "Wilson disease: Treatment and prognosis".)

  Although life expectancy for untreated patients with Wilson disease is uncertain, lack of pharmacologic therapy and/or liver transplantation generally results in progressive symptoms, liver failure with complications of portal hypertension, and death. (See 'Disease course' above.)

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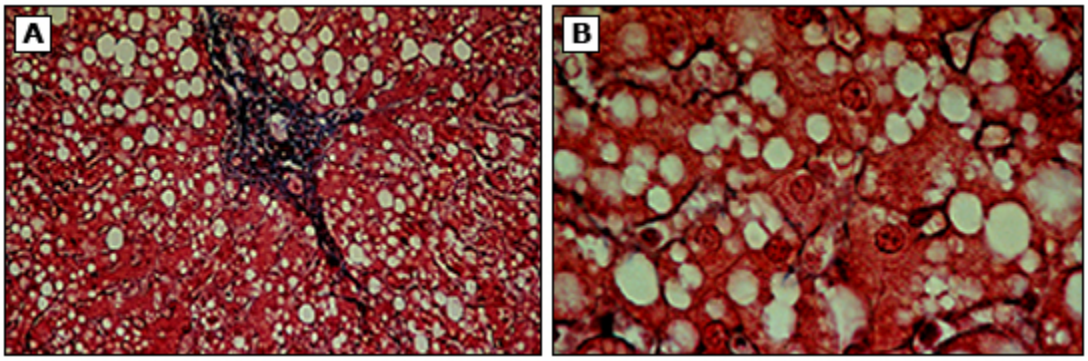
Topic 83837 Version 33.0

GRAPHICS

Wilson disease



Liver biopsy from a 4-year-old female patient whose 10-year-old sister presented with liver failure and cirrhosis secondary to previously unrecognized Wilson disease. Liver biopsy was performed because serum ceruloplasmin was low (4.0 mg/dL) and serum aminotransferases were repeatedly two to three times normal.

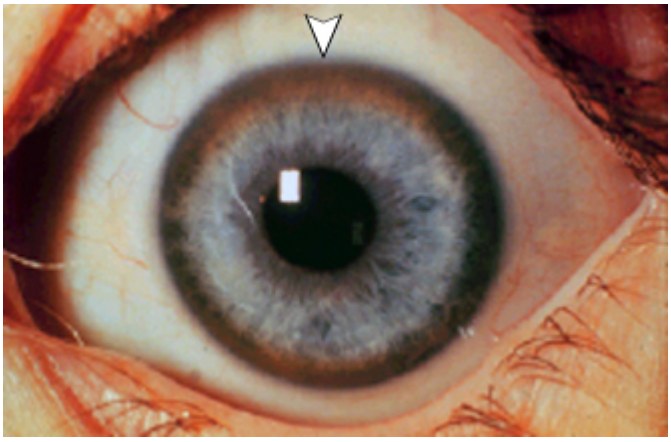
(A) Low power shows portal fibrosis, mild portal inflammation, and fatty infiltration (Masson trichrome).

(B) High power view shows fatty infiltration of hepatocytes and two glycogenated nuclei (Masson trichrome).

Courtesy of Marshall M Kaplan, MD.

Graphic 64346 Version 3.0

Kayser-Fleischer ring



Kayser-Fleischer ring (arrowhead) in a patient with advanced neuropsychiatric Wilson disease. The dense brown copper deposits encircle the iris. It is rare to see Kayser-Fleischer rings without the aid of a slit lamp examination because Wilson disease is usually recognized at an earlier stage when the rings are not as prominent.

Courtesy of Marshall M Kaplan, MD.

Graphic 65925 Version 3.0

Diagnostic testing for Wilson disease

Diagnostic test	Findings in Wilson disease	Comments
Slit lamp examination (or optical tomography)	▪ Kayser-Fleischer rings.	▪ Kayser-Fleischer rings are golden brownish rings that result from fine pigmented granular deposits of copper in Descemet's membrane in the cornea close to the endothelial surface.
24-hour urinary copper excretion	▪ A level >40 mcg/24 hours (>0.64 micromol/24 hours) is suggestive of Wilson disease and warrants further testing.	▪ To assess accuracy of the collection, we measure urinary creatinine excretion. ▪ 24-hour urine creatinine excretion should be between 15 and 20 mg/kg body weight. Values substantially above or below this estimate suggest over- and under-collection, respectively.
Serum ceruloplasmin	▪ Low level (<20 mg/dL [200 mg/L]).	▪ Ceruloplasmin is a 132-kd protein synthesized by hepatocytes and secreted into the circulation. ▪ Ceruloplasmin with bound copper is referred to as holoceruloplasmin (representing most of circulating ceruloplasmin), whereas ceruloplasmin that does not contain bound copper is referred to as apoceruloplasmin. ▪ Ceruloplasmin is an acute phase reactant and may be increased above basal levels with inflammatory states.
Serum copper concentration	▪ Typically low in proportion to the reduction in ceruloplasmin.	▪ In acute liver failure due to Wilson disease, copper may be markedly elevated (>200 mcg/dL [31.4 micromol/L]).
Liver biopsy	▪ Hepatic copper concentration is usually >250 mcg/g dry weight. ▪ Histologic findings may include fatty infiltration within hepatocytes,	

	glycogen inclusions within nuclei, and portal fibrosis.	
Genetic testing	▪ Biallelic, pathogenic (disease-causing) variants affecting both ATP7B alleles are required for the diagnosis.	▪ Wilson disease is an autosomal recessive disorder and is the result of mutation in *ATP7B*, a gene encoding a copper transport protein, ATP7B.
Brain imaging	▪ MRI findings include abnormal T2 signals in the basal ganglia, brainstem, and white matter.	▪ Brain imaging may be normal in patients with Wilson disease who do not have neuropsychiatric involvement.

This table summarizes diagnostic testing for evaluating patients with suspected Wilson disease. This table is intended for use in conjunction with additional UpToDate content. For more details, please refer to UpToDate topics on clinical features and diagnosis of Wilson disease.

MRI: magnetic resonance imaging.

Graphic 142021 Version 1.0

Laboratory findings in hemolysis and hemolytic anemia

Finding	Change in hemolytic anemia
Anemia*	Decreased hemoglobin Decreased hematocrit
Bone marrow response/recovery	Increased reticulocyte count Underestimation of HbA1C
Release of RBC contents	Increased LDH Increased indirect bilirubin Decreased haptoglobin Hemoglobinemia in intravascular hemolysis¶ Hemoglobinuria in intravascular hemolysis¶
RBC morphology changesΔ	Spherocytes or microspherocytes in immune hemolysis Schistocytes in microangiopathic hemolysis Blister or bite cells in oxidant injury Sickle cells in sickle cell disease Target cells and teardrop cells in thalassemia

Intravascular hemolysis often starts acutely and can be a medical emergency associated with DIC, AKI, and hypotension. Extravascular hemolysis can be chronic. Severe hemolysis can have intravascular and extravascular features. Values for HbA1C may be lower due to increased RBC turnover. Refer to UpToDate for details of the evaluation, interpretation of laboratory findings, use of the Coombs (antiglobulin) test, and management.

HbA1C: glycosylated (glycated) hemoglobin; RBC: red blood cell; LDH: lactate dehydrogenase; DIC: disseminated intravascular coagulation; AKI: acute kidney injury.

* The presence and severity of anemia depends on the degree of hemolysis and capacity of the bone marrow to compensate by increasing erythropoiesis.

¶ Intravascular hemolysis can be a medical emergency with free hemoglobin in the blood and associated with complications including DIC and acute renal failure. Findings associated with intravascular hemolysis may include schistocytes on the blood smear, hemoglobinemia (with red serum), hemoglobinuria (with dark or red urine), and hemosiderinuria in the urine sediment.

Δ Refer to UpToDate for additional details of these and other RBC morphologies and their implications.

Graphic 126234 Version 3.0

Leipzig scoring system for Wilson disease

Typical clinical symptoms and signs		Other tests	
KF rings		**Liver copper (in the absence of cholestasis)**	
Present	2	>5x ULN (>4 micromol/g)	2
Absent	0	0.8 to 4 micromol/g	1
Neurologic symptoms*		Normal (<0.8 micromol/g)	–1
Severe	2	Rhodanine-positive granules¶	1
Mild	1	**Urinary copper (in the absence of acute hepatitis)**	
Absent	0	Normal	0
Serum ceruloplasmin		1 to 2x ULN	1
Normal (>0.2 g/L)	0	>2x ULN	2
0.1 to 0.2 g/L	1	Normal, but >5x ULN after D-penicillamine	2
<0.1 g/L	2	**Mutation analysis**	
Non-immune (Coombs-negative) hemolytic anemia		On both chromosomes detected	4
Present	1	On one chromosome detected	1
Absent	0	No mutations detected	0
TOTAL SCORE	**Evaluation:**		
4 or more	Diagnosis established		
3	Diagnosis possible, more tests needed		
2 or less	Diagnosis very unlikely		

This scoring system includes clinical and laboratory testing. If information is missing for a given item, the patient is assigned 0 points for that item. Results are assigned to one of three categories: diagnosis of Wilson disease is highly likely; the diagnosis is probable, but confirmatory testing is warranted; or diagnosis is unlikely and other etiologies should be considered.

KF: Kayser-Fleischer; ULN: upper limit of normal.

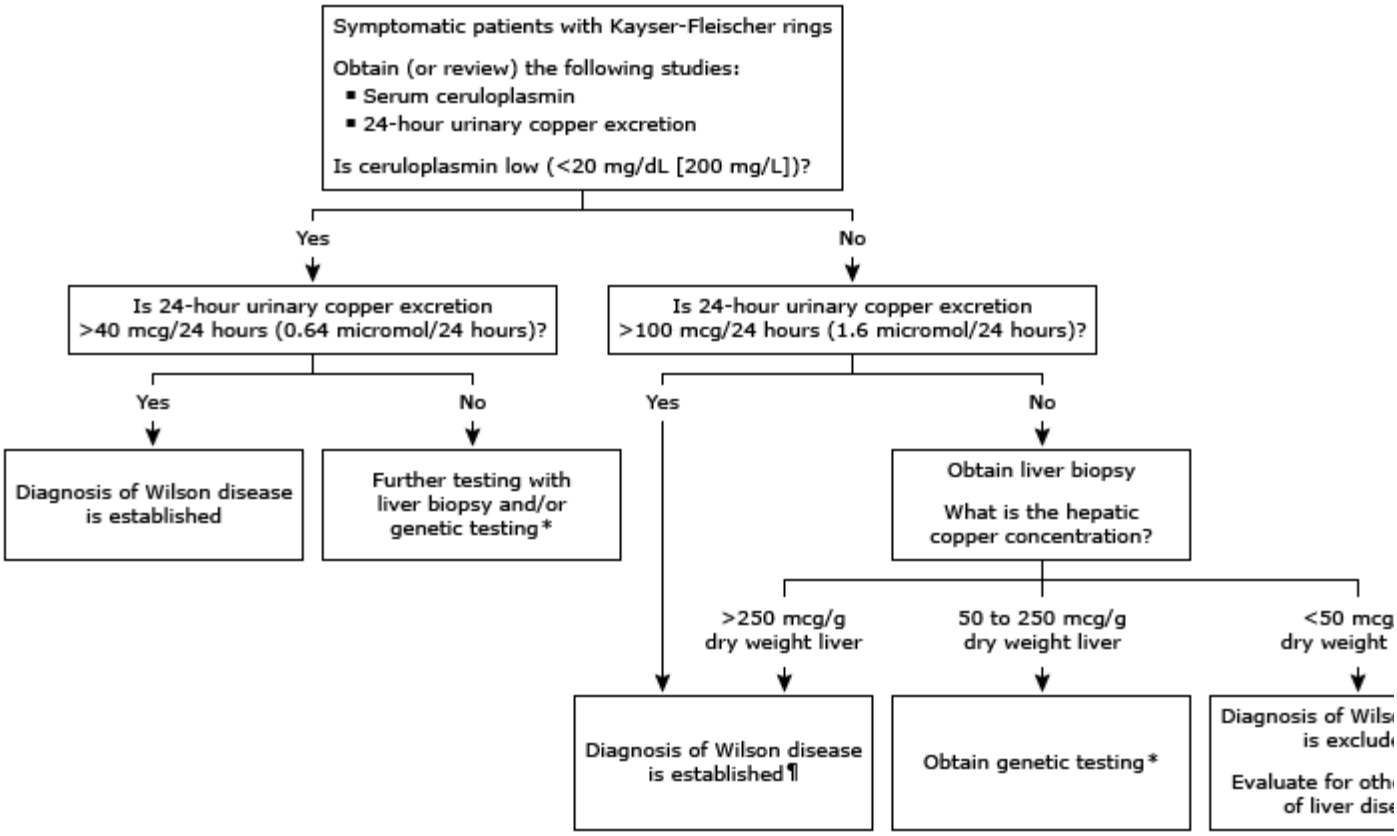
* Or typical abnormalities at brain magnetic resonance imaging.

¶ If no quantitative liver copper available.

Reproduced from: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol 2012; 56:671. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 105282 Version 2.0

Confirming the diagnosis of Wilson disease in patients with Kayser-Fleischer ri



This algorithm summarizes an approach to evaluating for Wilson disease in symptomatic patients (eg, eleva aminotransferases, low alkaline phosphatase, hepatomegaly) who have Kayser-Fleischer rings. This algorith intended for use in conjunction with UpToDate content on the clinical features and diagnosis of Wilson disea

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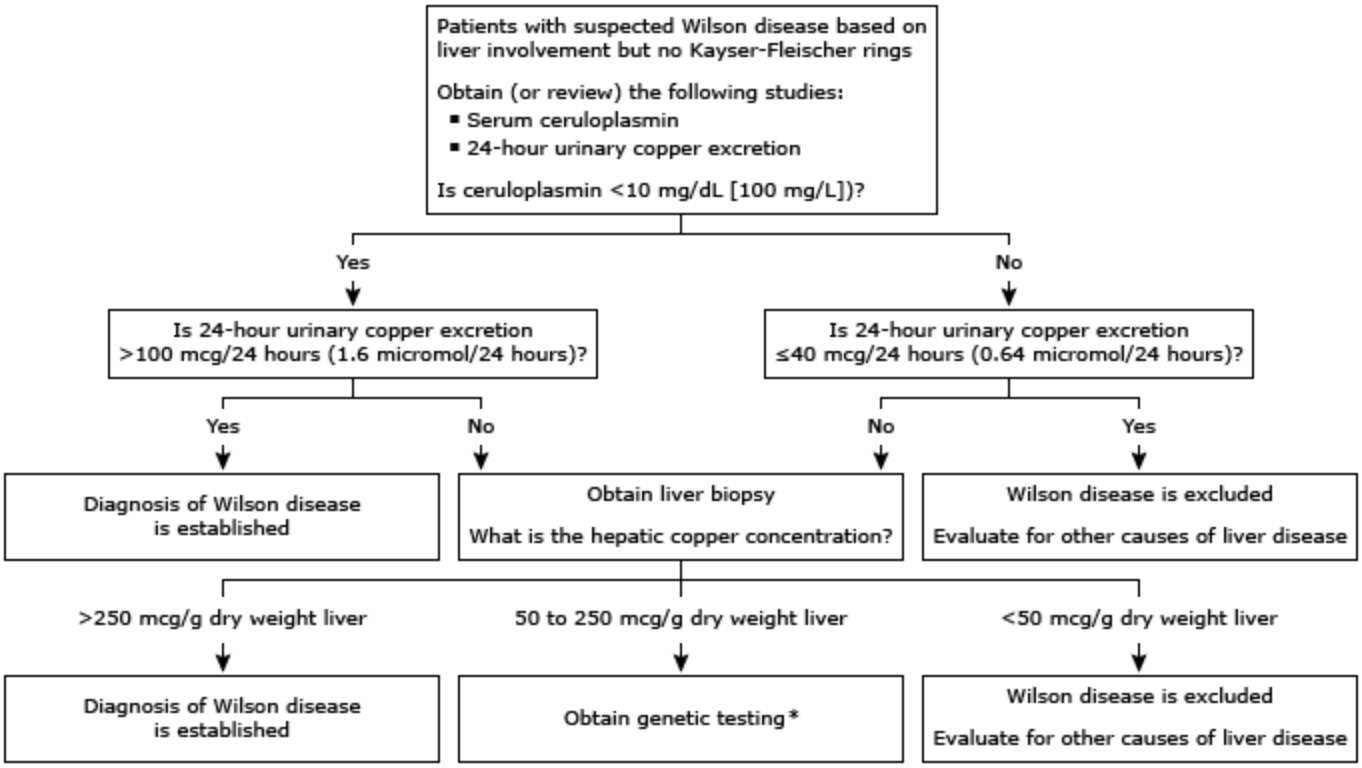
* Biallelic, pathogenic (disease-causing) variants affecting both ATP7B alleles are required to develop Wilson disease. Typically, one pathogenic variant is inherited from each parent. Most patients with Wilson disease a compound heterozygotes.

¶ For patients with discordant findings (ie, symptomatic patient with Kayser-Fleischer ring, elevated urinary excretion but normal ceruloplasmin), we typically obtain genetic testing also because normal ceruloplasmin uncommon in patients with Wilson disease.

Adapted from: Schilsky ML, Roberts EA, Bronstein JM, et al. A multidisciplinary approach to the diagnosis and management of Wilson 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases. Hepatology 2022.

Graphic 104976 Version 3.0

Evaluation of patients with suspected Wilson disease but no Kayser-Fleischer rings



This algorithm summarizes an approach to evaluating for Wilson disease in patients with liver-related symptoms (eg, elevated aminotransferases, low alkaline phosphatase, hepatomegaly) but no Kayser-Fleischer rings. Wilson disease may be suspected because liver findings are unexplained and/or accompanied by neurologic or psychiatric symptoms. This algorithm is intended for use in conjunction with UpToDate content on the clinical features and diagnosis of Wilson disease.

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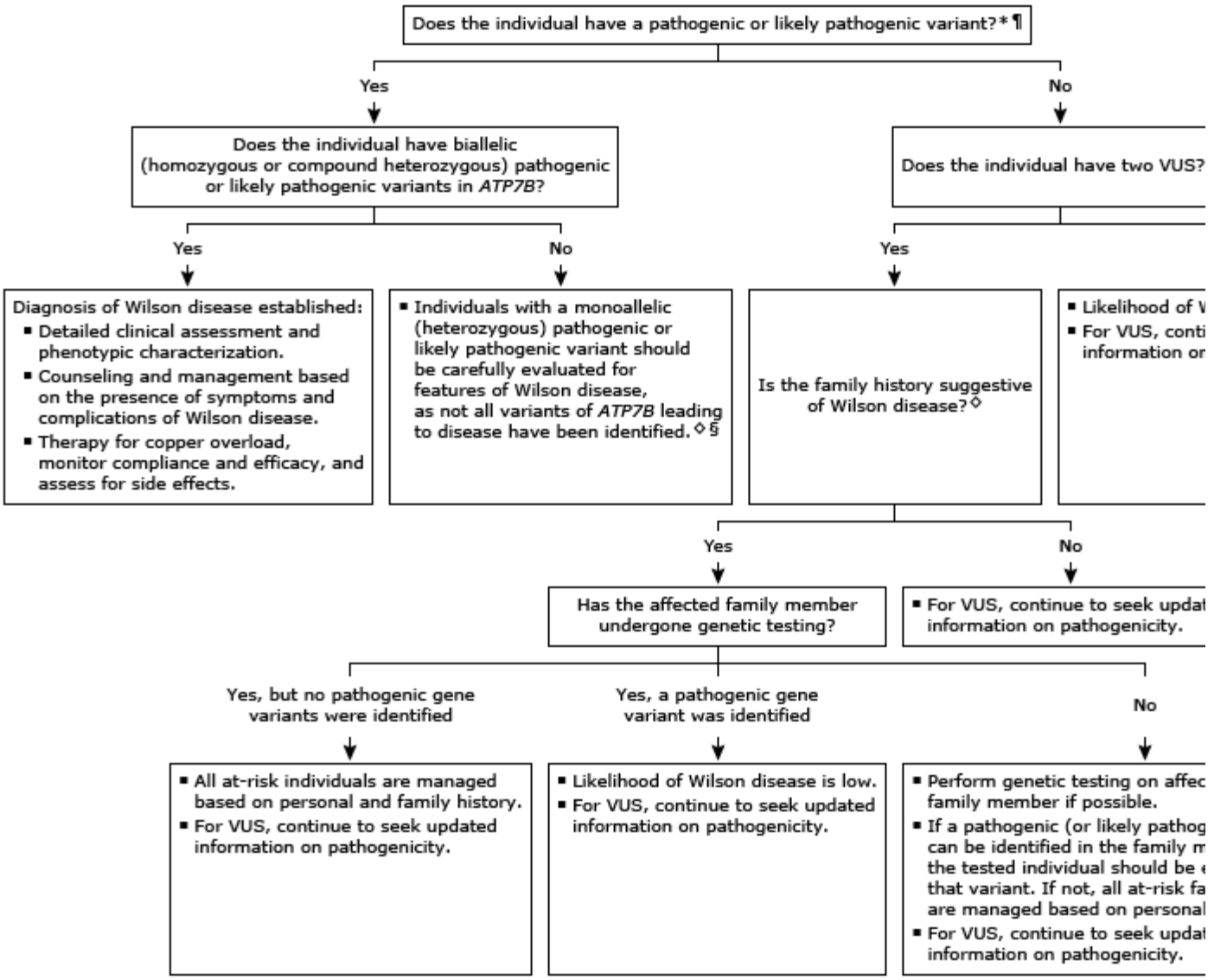
* Biallelic, pathogenic (disease-causing) variants affecting both ATP7B alleles are required to develop Wilson disease. Typically, one pathogenic variant is inherited from each parent. Most patients with Wilson disease are compound heterozygotes.

Adapted from: Schilsky ML, Roberts EA, Bronstein JM, et al. A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases. Hepatology 2022.

Graphic 141163 Version 1.0

Algorithm for a germline *ATP7B* genetic test result interpretation in individual
or symptoms of Wilson disease



This algorithm is only intended for individuals without signs or symptoms of Wilson disease. Interpretations pathogenicity may be revised as more data become available. It is especially important to seek this updated periodically for a VUS. Discussion with a genetic counselor and/or an expert in Wilson disease is likely to be most individuals with pathogenic or likely pathogenic variants in the *ATP7B* gene and/or a family history sug Wilson disease.

VUS: variant of uncertain significance.

* Ensure that the genetic testing is performed properly, the patient identification is correct, and the interpre pathogenicity is accurate based on the most recent data analysis.

¶ Pathogenic and likely pathogenic variants are treated the same for purposes of surveillance and risk redu interventions; these interventions are independent of family history.

Δ VUS lack sufficient information from clinical and bench research to be classified as pathogenic or benign. C seek updated interpretation of pathogenicity periodically (eg, annually).

◇ Wilson disease should be suspected in any patient with unexplained liver, neurologic, or psychiatric abnor first-degree relative of a patient with Wilson disease.

§ In patients with suspected Wilson disease initial evaluation includes liver biochemical tests, a complete blo serum ceruloplasmin and copper levels, an ocular slit-lamp examination, and a 24-hour urinary copper excr results of these tests determine the need for additional testing. Refer to related UTD content on the approa diagnosis of Wilson disease.

Graphic 133267 Version 1.0

Contributor Disclosures

Michael L Schilsky, MD, FAASLD Grant/Research/Clinical Trial Support: Alexion [Wilson disease]; Orphalan [Wilson disease]; Vivet [Wilson disease]; Wilson Disease Association [Wilson disease]. All of the relevant financial relationships listed have been mitigated. **Elizabeth B Rand, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Bruce A Runyon, MD, FAASLD** No relevant financial relationship(s) with ineligible companies to disclose. **Michael J Aminoff, MD, DSc** Consultant/Advisory Boards: Brain Neurotherapy Bio [Parkinson disease]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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