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

See online here

Wilson disease is an autosomal recessive inherited disorder related to copper metabolism. This rare condition is characterized by excessive deposition of copper in target organs like the liver, brain, etc.

Background

Wilson 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 disease is rare but important because it can be fatal if not recognized and treated opportunely.

Staging

Wilson disease consists of the following stages:

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

- Worldwide:
  - Incidence: 10–30 million cases
  - Heterozygote carrier rate: 1 in 100
  - Genetic mutation frequency: 0.3–0.7%
  - Fulminant presentation: More common in females

- United States:
  - Heterozygote carrier rate: 1 in 90
  - Prevalence: 1 in 30,000

- Japan
  - Prevalence: 1 in 30,000

- Australia
  - Prevalence: 1 in 100,000

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 below 3 years and in adults over 70 years.

Note: Always think about Wilson 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. This differential diagnosis should always be considered in patients with unexplained chronic liver disease, particularly persons between 5–40 years old. The 3 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 1–3 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...](image-url)
Fifty percent of patients with Wilson 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 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%): choreathetoid abnormal movements with dystonia

Psychiatric symptoms like emotional lability, impulsiveness, disinhibition, and self-injurious behavior are seen in 10–20% of patients with Wilson disease. These symptoms are 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, with 20–50% of patients showing joint involvement late in the course of the disease. The arthropathy involves the spine and large appendicular joints, such as the knees, wrists, and hips. Further, osteochondritis dissecans, chondromalacia patellae, and chondrocalcinosis have been reported.

**Hematologic symptoms**

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

**Renal symptoms**

Wilson 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 can also occur. 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 disease.

Physical Examination

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
- Mask-like 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) may also be noted.

Differential Diagnoses of Wilson’s Disease

- Acute Liver Failure
- Arthritis from different etiology
Workup

Kayser-Fleischer rings and ceruloplasmin of < 20 mg/dL with neurologic symptoms suggest Wilson disease. Isolated liver disease with a hepatic copper concentration of > 250 mg/g of dry weight and a low serum ceruloplasmin level are enough to establish the diagnosis of Wilson 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 disease must be screened.

Abdominal imaging

Computed axial tomography, 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

Ninety-percent of individuals with Wilson disease have ceruloplasmin levels of < 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 > 100 µg/d (reference range, < 40 µg/d) in most patients with symptomatic Wilson disease.

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

Radio-labeled copper
Radio-labeled copper testing of hepatic copper metabolism with blood collected at 1, 2, 4, 24, and 48 hours after oral ingestion of radio-labeled copper (64Cu or 67Cu) can be employed. 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
Cranial lesions are classified into 2 categories: well-defined, slit-like, 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 in detecting early lesions of Wilson disease. MRI studies can identify focal abnormalities in the white matter, pons, and deep cerebellar nuclei, measuring 3–15 mm in diameter, typically bilateral, representing cell loss and gliosis.

Positron emission tomography
Positron emission tomography exposes a reduced 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 perportal 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 that favor a negative copper balance. The patient needs to be aware of the potential adverse effects of these agents, especially with regard to 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’s disease.

Diet

The patient should avoid eating foods with 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 a copper content of < 0.2 parts per million.

Pregnancy

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

Pediatric

Pediatricians should consider Wilson disease in any child with hepatic abnormalities that require pediatric gastroenterologist consultation if suspicion remains high.

Geriatric

Geriatric patients with Wilson disease who are untreated will most likely present with fulminant hepatic failure or 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 with 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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