

Medical Writers' Circle

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Wilson's Disease: a Genetic but Treatable Liver Disorder

SUMMARY

Wilson's disease is a rare inherited metabolic disease that leads to copper accumulation mainly in the liver and brain. Although the accumulation of copper begins at birth, symptoms of the disorder appear later in life, between the ages of 6 and 40. The primary consequence in about 40 percent of patients with Wilson's is liver disease. In other patients the first symptoms are either neurological or psychiatric or both. Without proper treatment, Wilson's disease is generally fatal, usually by the age of 30. If treatment is begun early enough, symptomatic recovery is usually complete, and a life of normal length and quality can be expected. Although in most cases a well-timed treatment can solve both hepatic and neurologic signs, still few patients fail to respond to the current therapy. Some will require liver transplantation which will ultimately cure the disease by correcting the expression of the genetic defect in the liver.

INTRODUCTION

Wilson's disease (WD) is an inherited (autosomal reces-

sive) copper accumulation disorder that affects about 30 individuals per million,¹ but its frequency increases in populations where blood kinship is more common.² The disease is caused by the dysfunction of a liver enzyme or protein that transports copper (copper-transporting P-type ATPase) that has a crucial role in copper elimination from the body by excretion into bile.³⁻⁵ The gene encoding this protein, is located on the chromosome 13 (13q14.3) and there are numerous gene mutations that can impair the protein's function,^{6,7} leading to copper accumulation mainly in the liver, but also in the brain, eye (cornea) and kidney.

CLINICAL FEATURES

Most patients with WD are diagnosed between the first and the fourth decade of life,⁸ although the age at presentation can vary from 3 to 70.⁹ The main clinical features of WD include hepatic, neurologic and psychiatric symptoms and signs (*Figure 1*).

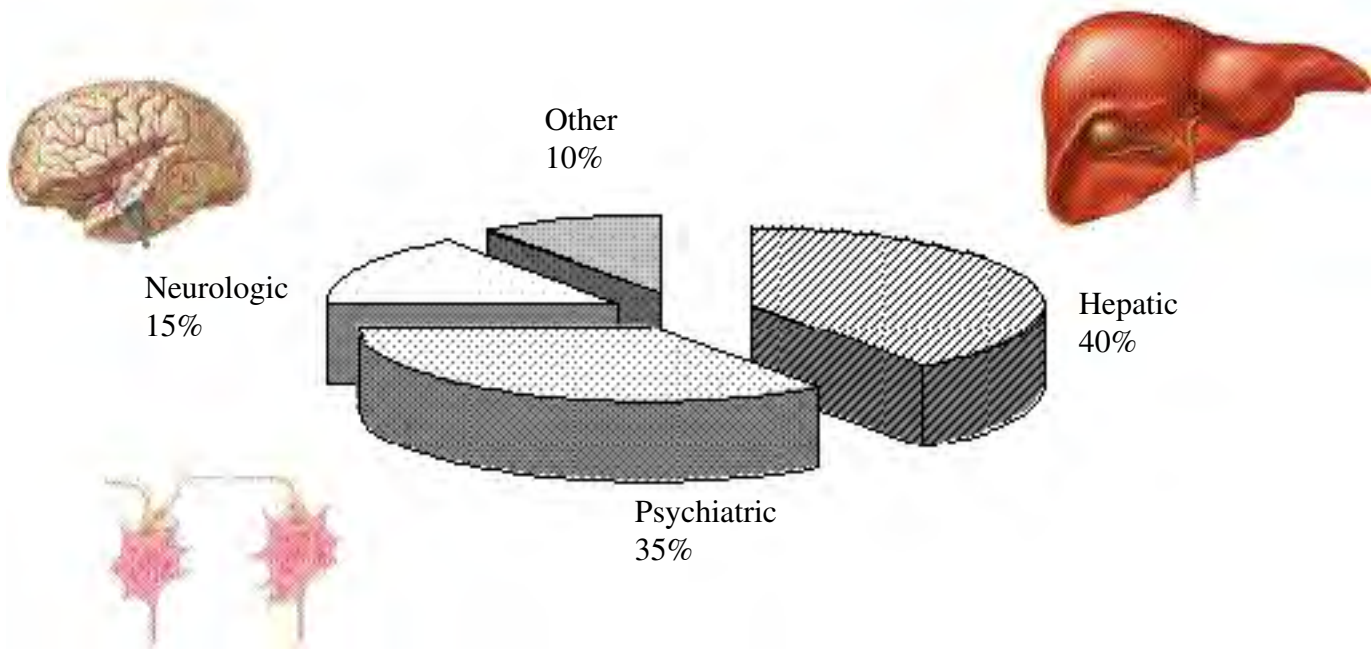
1. Liver involvement can vary from asymptomatic to hepatomegaly, fatty liver, and acute hepatitis (40% of cases) with

elevated serum transaminase levels, liver failure, jaundice, cirrhosis, and liver cancer. During acute liver failure, hemolysis can also occur.

2. Neurologic disturbances, which usually present in the third decade of life, are the initial symptoms of WD in approximately 40–50 % of patients.¹⁰ Typical symptoms are slow (hypokinetic) or difficult speech, tremor, dystonia (abnormal tonicity of muscle, characterized by prolonged, repetitive muscle contractions), incoordination and difficulty in swallowing (dysphagia). The patient may show symptoms similar to Parkinson's disease because the copper typically accumulates in the basal ganglia, which are the areas of the brain affected by Parkinson's.

3. Up to 5 years prior to hepatic or neurologic manifestations, patients can develop psychiatric and behavioral abnormalities, such as depression (sometimes leading to attempted suicide), paranoia, hallucinations and delusions, irritability, reduced sexual inhibition, and reduced performance at school or at work.¹¹ Behavioral and cognitive symptoms can be reversed by 1–2 years of continuous treatment.¹²

Figure 1. Clinical features of Wilson's disease at disease onset.



4. Heart, kidney, bones and hormonal glands can also be affected in WD in fewer than 10% of patients. Endocrine features of WD include changes in the metabolism of calcium (hypoparathyroidism),¹³ menstrual irregularities and infertility.¹⁴ Renal features include kidney stones (nephrolithiasis) and loss of small proteins in the urine (aminoaciduria).¹⁵ Cardiac features include weakness of the heart muscle (cardiomyopathy) and abnormal rhythm (dysrhythmias).¹⁶ Skeletal features include arthritis and premature bone loss (osteoporosis).¹⁷

When Wilson's disease has to be suspected?

- Unexplained liver disease: liver enzyme/test abnormalities (ALT, AST), enlarged liver (hepatomegaly), or features of chronic liver disease, at any

age of presentation

- Unexplained neurologic and/or psychiatric disease, at any age of presentation
- Family history: first-degree relative diagnosed with WD.

DIAGNOSIS

Hepatic copper

In almost all patients with WD the liver copper content is greater than 250 microgram (µg) per gram of dry weight (normal: <50µg/g d.w.) and can be as high as 3,000 µg/g.¹⁸ Occasionally, patients who have severe cirrhosis have a liver copper content of less than 250µg/g, because of the uneven distribution of copper in the liver. Histochemical methods (i.e., copper staining in the liver tissue) for the detection of excess copper in

the liver are unreliable.¹⁹ Obviously both methods require a liver biopsy that is a relatively invasive, potentially dangerous, and sometimes painful procedure.

24-hour urinary copper

A urinary copper greater than 100 µg/24 hours (>1.6 µmoles/24 hours) is considered diagnostic for WD. This level is reached in most symptomatic patients, but a level of 40–100 g does not exclude the diagnosis of WD in asymptomatic patients, and they therefore require further testing.¹⁸

Ceruloplasmin

Ceruloplasmin is a copper-carrying protein. It is bound to 90% of the circulating copper in normal individuals. The normal concentration of

ceruloplasmin is 20–50 mg/dL, and a serum ceruloplasmin level less than 20 mg/dL is considered diagnostic for WD. The clinical utility of this measurement is limited by the fact that normal ceruloplasmin concentration is found in about 20% of WD patients.

Kayser-Fleischer rings

Kayser-Fleischer rings are a particular copper-like coloring of the cornea, that may be seen with naked eye, but more often requires a special exam performed by the eye doctor (the slit lamp examination).

The presence of Kayser-Fleischer rings indicates that free copper has been released into the circulation. Kayser-Fleischer rings are present in 50–60% of patients with mainly hepatic disease, and in 90–95% of patients with

mainly neuro-psychiatric involvement.²⁰ Kayser-Fleischer rings are not found in all WD patients and they are not completely specific for the disorder either: they can be found in

“Most patients with WD are diagnosed between the first and the fourth decade of life, although the age at presentation can vary from 3 to 70.”

patients with neonatal or adult acute or chronic liver diseases with obstruction of the bile flow (cholestasis).²¹ Another rarer finding is sunflower cataracts, which represent deposition of copper in the lenses of the eyes.

Serum copper

The plasma free copper concentration (i.e., copper not bound to ceruloplasmin) is considered useful for the diagnosis of WD, but, to calculate its value, the total concentration of copper and ceruloplasmin in plasma must be measured. Considering that the amount of copper bound to ceruloplasmin is about 3µg per milligram of ceruloplasmin, the serum free copper concentration is calculated by the difference between the serum copper concentration (µg/dL) and 3 times the ceruloplasmin concentration (mg/dL).²² The serum free copper concentration is greater than 25 µg/dL in most untreated patients (normal value <15 µg/dL).

Genetic testing

Genetic testing is not prime time yet. At present, more than 200 mutations of the gene (*ATP7B*) have been identified,

but results on phenotype–genotype correlation are not yet conclusive, probably due to the high number of compound heterozygous alleles or the presence of environmental factors that contribute to the phenotypic expression. Detecting disease-causing mutations allows WD to be diagnosed, but a negative result cannot exclude a diagnosis of WD. The use of genetic testing should therefore be limited to screening first-degree relatives of patients with WD.

How to proceed with the work up for Wilson’s disease? (see also Table 1)

- Always keep a high index of

suspicion

- Wilson’s disease can be diagnosed in all age groups
- There is no gold standard for diagnosis, which is based on

a combination of clinical and laboratory findings

- The key findings are urinary copper levels >100 µg/24h, hepatic copper levels >250 µg/g d.w., ceruloplasmin levels < 20 mg/dL and Kayser-Fleischer rings

THERAPY

Diet

Foods rich in copper (e.g., liver, chocolate, nuts, mushrooms and shellfish) should be avoided, at least in the first years after diagnosis. More stringent dietary measures are unpleasant, impractical and probably do not delay the pro-

gression of disease.²³ Drinking water usually contains less than 0.2 mg copper per liter and therefore there is no need to use distilled water.

D-Penicillamine

D-Penicillamine (D-PCA) mobilizes copper by making copper–penicillamine complexes (chelating action) that are excreted in the urine. Most patients with mainly hepatic WD experience a clinical improvement after 6–8 weeks of treatment, but it can take 6–12 months for changes to be noticeable.²⁴ It is recommended that patients be started on lower doses, followed by gradual dose increments to the therapeutic range in order to improve tolerability.²⁵ D-PCA can induce a vitamin B6 deficiency so a daily dose of 25 mg pyridoxine (vitamin B6) is usually added to the treatment regimen.

Approximately 30% of patients have allergic or hypersensitivity reactions in the first month of treatment including: fever, skin rash and enlargement of lymph glands (lymphadenopathy).²⁵ A more-serious early reaction is bone marrow depression which can present as severe anemia (aplastic), low white cell (neutropenia) and low

Table 1. Tests for the diagnosis of Wilson’s disease

| Test | Typical findings | Normal range |
|------------------------|-----------------------|----------------|
| Hepatic copper | > 250 µg/g dry weight | < 50 µg/g d.w. |
| 24-h urinary copper | > 100 µg/24 h | < 40 µg/24 h |
| Serum ceruloplasmin | < 20 mg/dL | 20-50 mg/dL |
| Kayser-Fleischer rings | present | absent |
| Serum free copper | > 25 µg /dL | < 15 µg /dL |

platelet (thrombocytopenia) counts. Late drug reactions can be seen even after years of uneventful treatment. The most common of these late side effects involve the skin (degenerative change, *elastosis perforans serpiginosa*)²⁶ and joints (arthropathy), or are mediated by immunological effects (lupus-like reaction, nephrotic syndrome, myasthenia gravis, Goodpasture syndrome).²⁵ Neurological symptoms reportedly become more severe in about 50% of patients taking D-PCA.²⁷

Trientine

Trientine is a copper chelator, acting primarily by enhancing urinary copper excretion. It is used as an alternative to D-PCA, in case of D-PCA intolerance. It is thought to act by mobilizing tissue copper, although at a lesser degree compared with D-PCA.²⁸ Trientine is probably less toxic

than D-PCA. Late adverse reactions include lupus-like syndrome with loss of proteins in the urine (proteinuria), and moderate anemia (sideroblastic).²⁹ The risk of neurological worsening is reported to be lower than 20%.³⁰

Zinc

Zinc increases the levels of an intestinal protein (metallothionein),^{31, 32} which also has high affinity for copper. The tight linkage between copper and metallothionein inhibits further copper absorption (“mucosal barrier”) and promotes its loss in the stools as intestinal cells are shed during normal turnover. Zinc may also increase metallothionein levels in liver cells. Copper binding to metallothionein may produce non-toxic complexes in the liver with little or no change in the total hepatic copper concentration, but with reduced toxicity.³³ Zinc is mainly used

as first-line therapy in case of (a) presymptomatic or asymptomatic patients,³⁴ (b) during maintenance therapy, and (c) for patients with mainly neuropsychiatric involvement, as neurologic worsening is very uncommon during zinc therapy (10% in our experience).

Zinc is generally well tolerated. Gastric irritation is the most frequent problem (10–15 %),³⁵ but it can be obviated by substituting zinc sulfate with zinc acetate or by taking the first daily dose mid-morning rather than before breakfast.

Tetrathiomolybdate

Tetrathiomolybdate has two mechanisms of action.³⁶ First, it binds copper in the intestinal lumen and prevents its absorption. Second, once absorbed, it complexes copper and albumin in the blood and makes the copper unavailable for entering cells. Tetrathiomolybdate has been proposed as

initial treatment for patients presenting with neurologic signs and symptoms.³⁷ It is not commercially available in either the US or the European Union, and there is very limited clinical experience to recommend its use. Recently a randomized, double-blind, controlled study of 48 WD patients with neurological presentation was performed: patients were treated with trientine or tetrathiomolybdate for 8 weeks.³⁸ Patients treated with tetrathiomolybdate experienced less frequent neurologic deterioration compared with trientine, and about 15% of patients experienced side effects which were mild. Side effects include: bone marrow toxicity, such as anemia, low platelet and low white cell count, and elevation of liver enzymes. Both were described as transient and reversible after drug discontinuation.

Table 2. Wilson’s disease pharmacological treatment

| Drug | Dose | Indication | Side effects |
|------------------|----------------|--|--|
| DPCA | 1-1.5 g/day | Hepatic WD | Hypersensitivity reactions, bone marrow depression, late reaction involving skin, joints and immune system. Neurological worsening |
| Trientine | 1 g/day | Hepatic and Neurologic WD (in case of DPCA intolerance) | Lupus-like syndrome, sideroblastic anemia. |
| Zinc | 150-200 mg/day | Hepatic and neurologic WD: pre-symptomatic and/or maintenance; pregnancy | Gastric discomfort |

Legend: DPCA, D-Penicillamine; TTM, Tetrathiomolybdate; WD, Wilson’s disease

Liver Transplantation

Liver transplantation is the ultimate treatment for patients with WD. Survival rates reportedly range from 100% at 33 months³⁹ to 62% at 1 year.⁴⁰ We have reported overall patient survival rates of 89% at 6-12 months and of 76-59% at 5-10 years.⁴¹

WD patients should be considered for liver transplantation only after suitable medical therapy has failed. Patients with a combination of hepatic and neuro-psychiatric conditions deserve careful neurologic evaluation; liver transplantation is contraindicated only in cases of severe neurological impairment. Neuro-psychiatric symptoms alone are a contraindication for liver transplantation.⁴²⁻⁴⁴

Patients with WD who develop acute liver failure should be immediately referred to a liver transplant center, since survival without transplant in these acute cases is practically zero.⁴⁵

Practical guidelines for the treatment of Wilson's disease (see also Table 2)

- Start therapy as soon as possible: Wilson's disease is a treatable disorder
- Initial treatment of symptomatic patients who have only hepatic involvement should include a chelating agent (D-PCA or trientine)
- Treatment of presymptomatic patients or maintenance therapy of patients with mainly hepatic involvement can be safely based on zinc salts
- Patients with mainly neuro-

psychiatric involvement should be treated from the beginning with zinc, and never with D-PCA

- Liver transplantation represents the ultimate treatment for Wilson's disease, when all medical therapies options fail, but neuro-psychiatric disease as the main clinical symptom is a contraindication to orthotopic liver transplantation.

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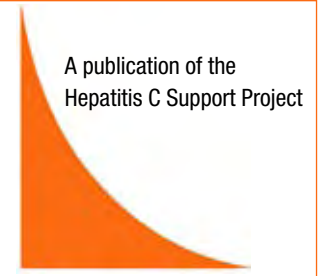
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Disclosure

The Division of Gastroenterology and Hepatology of the UC Davis Medical Center is a Regional Referral Center for patients with Wilson's Disease, as designated by The Wilson's Disease Association International.

If you are/have a patient with Wilson's and would like to refer to Drs. Medici or Rossaro, please contact 1-800-4UCDavis (482-3284)(for Providers) or 1-800-2UCDavis (282-3284) (for Patients).



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