Wilson disease: more than meets the eye

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ABSTRACT

Wilson disease is a rare but important disorder of copper metabolism, with a failure to excrete copper appropriately into bile. It is a multisystem condition with presentations across all branches of medicine. Diagnosis can be difficult and requires a high index of suspicion. It should be considered in unexplained liver disease particularly where neuropsychiatric features are also present. Treatments are available for all stages of disease. A particularly important presentation not to overlook is acute liver failure which carries a high mortality risk and may require urgent liver transplantation. Here, we provide an overview of this complex condition.

INTRODUCTION

Wilson disease (WD) was first described in 1912 as a progressive, ultimately fatal hepatolenticular degeneration accompanied by cirrhosis. Later, it was identified as a condition of impaired copper metabolism, where a failure to excrete copper in bile leads to hepatic accumulation. This is due to a defective copper transport protein mapped on the *ATP7B* gene on chromosome 13. The gene was recognised in 1993.¹ Oral therapy, in the form of copper chelators, was developed in the 1950s by Dr John Walshe.

Most copper absorption occurs at the duodenum and proximal small intestine. Copper is transported to the liver and thereafter used for liver metabolism and synthesis of caeruloplasmin (CP). Additionally, copper is important in the mobilisation of tissue iron stores. Intracellular copper binds to various substances such as metallothionein which helps to prevent cellular damage by transferring or storing the copper to be used intracellularly, by incorporating it into CP or by excreting it into bile. Biliary excretion of copper is dependent on *ATP7B* transporter.^{2–5} A defect in this pathway due to a mutation of *ATP7B* leads to copper accumulation. A balanced diet normally provides an excess of the body's total daily copper requirements. Although small, this daily excess leads to significant accumulation in WD.

WD is seen across all populations, with a gene frequency of 1 in 90–150 and an incidence of 1 in 30 000.⁶ More than 500 distinct mutations have been described in the gene, from which 380 have a confirmed role in the pathogenesis.⁶ WD can present at any age, although most will be diagnosed between 5 and 35 years. Most patients are compound heterozygotes making genotype to phenotype correlation challenging.

CLINICAL MANIFESTATIONS

Excess accumulation of copper initially occurs in the liver leading to oxidative stress of hepatocytes

resulting in oxidative damage and leading to deranged liver function tests, hepatic steatosis, acute hepatitis, hepatic fibrosis, cirrhosis or acute liver failure (ALF). Patients with WD often present with hepatic or neuropsychiatric manifestations. Clinically, many patients will remain asymptomatic for many years but the ongoing hepatic burden of copper accumulation may present in clinical practice with organomegaly and peripheral stigmata of chronic liver disease. Not uncommonly, patients may present with decompensated cirrhosis manifesting as jaundice, encephalopathy, ascites and acute upper gastrointestinal bleeding. WD should be considered in all patients with unexplained liver disease, especially in those with family history of WD or in those who do not respond as expected to standard treatments, for example, immunosuppression in autoimmune hepatitis (box 1).

Damaged hepatocytes release copper into the blood where it can be deposited in other organs, particularly the brain, for example, basal ganglia midbrain, pons, thalami and cerebelli leading to the neurological sequelae associated with WD which often resemble movement disorders (table 1). Psychiatric symptoms also range widely (table 1) and are more common in patients with neurological than hepatic involvement.^{7,8} Accumulation of copper in other tissues may lead to further non-hepatic, non-neuropsychiatric complications. For example, excess amounts of copper in red blood cells (RBCs) may lead to Coombe's negative haemolytic anaemia.

Box 2 highlights the possible involvement of other organs in the WD and the multitude of clinical manifestations which may contribute towards the clinical presentation of patients.^{9,10}

DIAGNOSIS

Kayser-Fleischer (KF) rings

The presence of KF rings are regarded by some as a classic hallmark of the disease. They are seen in 50%–60% of patients with isolated hepatic WD and in more than 90% of patients with neurological involvement.¹¹ Their pathophysiology involves copper deposition in the Descemet's membrane in the cornea. Slit-lamp examination is diagnostic. They are, however, not specific and they have been reported in other chronic cholestatic diseases.

Caeruloplasmin (CP) levels

CP is a glycoprotein synthesised by hepatocytes in the liver and is the major copper-containing protein in the blood. Once containing its bound complement of copper (six atoms per molecule), CP is referred to as holocaeruloplasmin and represents the majority of circulating CP in healthy individuals. The defect in WD causes a failure of copper

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Box 1 Presentations that could suggest Wilson disease (WD)^{15 33}

1. First degree relative of a patient with WD.
2. Non-alcohol fatty liver disease/non-alcohol steatohepatitis with atypical features (eg, young age).
3. Autoimmune hepatitis non-responsive to treatment (particularly in children).
4. Acute liver failure (especially with haemolysis).
5. Any unexplained liver disease, particularly with neurological or psychiatric symptoms.

incorporation into apocaeuloplasmin which is degraded more rapidly, and therefore steady state serum CP levels are reduced. A serum CP concentration below the laboratory lower limit (usually 20 mg/dL; 0.2 g/L) with the presence of KF rings is considered diagnostic of WD.¹² However, serum CP may be low in some patients without WD and may be normal or even elevated in the minority of patients with WD.¹¹ Most reports based on several decades of experience from the mid-1950s onward indicate that 90%–100% of patients had serum CP in the subnormal range.¹² Overall, serum CP alone is not sufficient to diagnose or to exclude WD.

HAEMOLYSIS

Coombs-negative haemolytic anaemia may accompany WD. Marked haemolysis is commonly associated with severe liver disease. Even though the exact mechanism for this is not known, it is believed to be secondary to copper accumulation in RBCs and possible oxidative destabilisation of the cellular membrane of RBCs. Hepatocyte necrosis may result in the release of stored copper, further aggravating haemolysis. In patients with ALF due to WD, haemolysis with a haemoglobin <100 g/L is not uncommon.¹³

LIVER BIOPSY

A liver biopsy is required if the clinical signs and non-invasive tests do not confer a diagnosis or if there is suspicion of other coexisting liver pathologies. Biopsies should be sent to histology as well as for hepatic copper quantification. The specimen for copper quantitation should be at least 1 cm and placed in a dry, copper-free container.

Quantitative hepatic copper determination in patients with WD usually reveals >250 µg (4 µmol) of copper per gram of dry weight (normal <50 µg (0.8 µmol)).¹⁴ There can be variability in copper distribution within the liver, contributing to sampling error particularly among patients with cirrhosis which may lead to a falsely normal hepatic copper quantification.¹⁴

Table 1 Potential neurological and psychiatric manifestations of Wilson disease

Neurological manifestations ³⁴	Behavioural and psychiatric manifestations ^{6 35}
Dysarthria	Depression
Dystonia	Poor educational achievement
Tremor	Personality change
Cognitive dysfunction	Psychosis
Ataxia*	Irritability
Parkinsonism*	Labile mood
Chorea*	

*Usually do not occur in isolation.

Box 2 Other manifestations of Wilson disease^{9 10 36}

- ▶ Renal involvement
 - Nephrocalcinosis
 - Haematuria
 - Aminoaciduria
 - Basement membrane changes
 - Renal tubular acidosis
- ▶ Musculoskeletal involvement
 - Osteoporosis
 - Osteomalacia
 - Osteoarthritis
 - Chondrocalcinosis
 - Myopathy
 - Arthralgia
- ▶ Cardiac involvement*
 - Cardiomyopathy
 - Arrhythmias

*Rarely clinically evident.

Thus, hepatic copper should always be evaluated in the context of other diagnostic criteria. WD cannot be excluded solely on a hepatic copper concentration <250 µg/g (4 µmol/g), but can be excluded if the hepatic copper concentration is <50 µg/g dry weight (0.8 µmol/g dry weight). On the other hand, a copper concentration >250 µg/g is virtually diagnostic unless the patient has chronic cholestatic liver disease, which is usually clinically distinguishable from WD.

If the hepatic copper concentration is between 50 and 250 µg/g dry weight, especially if histology reveals evidence of active liver disease, molecular genetic testing for *ATP7B* mutations is indicated.

COPPER TESTS

Serum copper measures both CP and non-CP bound copper (NCC). NCC is usually bound to albumin or amino acids. In healthy individuals, NCC represents only around 10% of total copper levels but is raised in WD. Despite being a disorder of copper overload, the total serum copper in WD is usually decreased, in proportion to the decreased circulatory CP, despite this higher NCC level. In those with severe liver injury, serum copper may be within the normal range, independent of serum CP levels. In ALF due to WD, serum copper may be elevated due to the sudden release of copper from hepatocytes. This challenging interpretation of serum copper probably explains why copper levels are infrequently used as scoring parameters in the major diagnostic algorithms.^{6 15} While there are assays available for NCC measurement, they require validation.¹⁶ Thus, NCC is usually calculated according to the following formula:¹⁷

$$\text{NCC (}\mu\text{g/dL)} = \text{serum copper (}\mu\text{g/dL)} - (3.15 \times \text{serum CP (mg/dL)})$$

Calculation of NCC is not incorporated into diagnostic criteria as it relies on accuracy of copper and CP measurements which can overestimate holocaeuloplasmin leading to a negative number.

Urinary copper excretion, however, is useful for the diagnosis of WD, typically associated with 24 hours urinary copper excretion of >1.6 µmol, although lower values have been described in up to 25% of asymptomatic patients with confirmed disease¹⁸ and in children and asymptomatic siblings.¹⁸ A value >0.64 µmol/day raises the possibility of WD and warrants further

Table 2 Leipzig Score³⁷ for the diagnosis of Wilson disease

Kayser-Fleischer rings	
Present	2
Absent	0
Neurological symptoms or typical imaging at brain MRI	
Severe	2
Mild	1
Absent	0
Serum caeruloplasmin	
Normal (>0.2 g/L)	0
0.1–0.2 g/L	1
<0.1 g/L	2
Coombs negative haemolytic anaemia	
Present	1
Absent	0
Liver copper (in the absence of cholestasis)	
> ×5 ULN (>4 µmol/g)	2
0.8–4 µmol/g	1
Normal (<0.8 µmol/g)	-1
Rhodanine-positive granules *	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1–2× ULN	1
>2 ULN	2
Normal, but >5 × ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes	4
On one chromosome	1
No mutation detected	0

Total score: 4 or more, diagnosis established; 3, diagnosis possible, more tests needed; 2 or less, diagnosis very unlikely.

*If no quantifiable copper available.

investigation. The test should not be used in patients with renal failure.

Urinary copper excretion with D-penicillamine administration was thought to be a useful diagnostic test. This test has only been standardised in a paediatric population (thus is not recommended for diagnosis in adults) in which 500 mg of D-penicillamine is administered orally and again 12 hours later during the 24 hours urine collection.

GENETIC TESTING

There are many mutations and comprehensive molecular genetic testing takes months, making this a difficult to use diagnostic test. However, molecular analysis of the ATP7B gene in any provisional diagnosis of WD for confirmation is recommended and for later screening of relatives. By contrast, allele-specific probes allow direct identification of a mutation and this can be rapid. However, this can only be accomplished if a mutation occurs with a reasonable frequency in the population. With the advancement of DNA-based diagnostics, it is expected that genetic testing will take on a more prominent role in any updated international guidelines. In the UK, sequencing of the entire coding region of the gene and targeted mutation analysis are only available through the Sheffield Diagnostic Genetics Service Laboratory.

The diagnosis of WD is challenging due to the heterogeneous clinical, biochemical and histological presentation of the disease. With this in mind, a diagnostic framework has been proposed which employs a scoring system based on seven parameters

which have been discussed above (table 2). Additionally, to allow more focused progression through these various investigations, we include a suggested diagnostic algorithm (figure 1).

FAMILY SCREENING

First-degree relatives of patients diagnosed with WD should be screened, with siblings having 25% chance of being homozygous and therefore having disease. The risk for the probands' offspring is less (0.5%); however, screening must still be performed. If the mutation of the proband is known, screening of siblings can be done with mutational analysis, which is more specific and economical than genotyping for polymorphisms of the WD gene. For a child of the proband, DNA is required from both parents. Haplotype analysis, based on the pattern of dinucleotide and trinucleotide repeats around ATP7B, can be determined in the index patient, allowing assessment of whether relatives are unaffected, heterozygous or affected.¹⁹ In the situation where genetic testing is not available, evaluation of a first degree relative with clinical and biochemical testing as for an individual with a suspicion of WD is recommended.

TREATMENT

Drug therapy was established in the 1950s. It is clear that all patients with a diagnosis of WD should receive treatment, regardless of the stage of disease. Symptomatic individuals should be treated with a chelator (D-penicillamine or trientine) as first-line therapy. The choice between chelators is dependent on clinician and patient preference and increasingly on financial grounds with the price of trientine rising leading to problems with access in the UK. Zinc therapy can be used after initial de-coppering when the patient is in maintenance stage of treatment or in dose presymptomatic individuals.

D-penicillamine

The major effect of D-penicillamine in WD is to promote the urinary excretion of copper, but it may also act by inducing metallothionein and interfering with pyridoxine action; hence, supplemental pyridoxine is often provided. The effectiveness of D-penicillamine in WD²⁰ has been described in numerous studies. Recovery of synthetic liver function and clinical improvement can be seen in the initial 2–6 months after initiation of therapy, with further recovery possible during the first year. It has been reported that advanced fibrosis and cirrhosis may have a degree of reversibility with prolonged therapy. It is important to be aware of reports of worsening of neurological symptoms in of patients treated with D-penicillamine during the initial treatment, but data are somewhat limited.

Tolerability of D-penicillamine may be enhanced by starting with low dose followed by uptitration; 125–250 mg/day increased by 250 mg increments every 4–7 days to a maximum of 1000–1500 mg/day in 2–4 divided dosages. The dose can be reduced to 15 mg/kg for maintenance therapy.

Side effects of D-penicillamine cause a change in therapy in about 25%.²⁰ Early side effects include hypersensitivity with fever and rash, marrow suppression and early paradoxical neurological worsening. Other reactions include a lupus-like syndrome with development of nephritis with severe protein loss, a Wegener's-like syndrome and myasthenia gravis as well as dermatological changes including elastosis perforans serpiginosa and progeric appearance. Colitis can occur rarely. Compliance is often a problem and can be assessed by measuring 24 hours urinary copper excretion. The amount of copper excreted in the urine will increase with increasing dosing of D-penicillamine.

Figure 1 Suggested diagnostic algorithm for diagnosis of WD (adapted from AASLD guidelines 2008.⁷ CP, caeruloplasmin; Cu, copper; KF, Kayser-Fleischer; WD, Wilson disease.

Monitoring on therapy includes a complete blood count, urinalysis and serum creatinine often after the first week, and then monthly for 3 months, at 3 month intervals until stable target values are achieved and twice per year thereafter.

Trientine dihydrochloride

Trientine is another chelator, however, there is a paucity of data on its pharmacokinetics. Data and clinical experience suggest Trientine is as effective for WD as D-penicillamine.²⁰ It is useful in patients who are intolerant of penicillamine as well as for primary therapy including decompensated liver disease. Trientine seems to have fewer side effects than D-penicillamine when used as primary therapy. The usual initial dose in children is 20 mg/kg per day, rounded to the nearest 250 mg, given in two or three divided doses. Similar dosing is used for adults.

Neurological worsening with treatment initiation is also seen with trientine, but appears to be less common than with D-penicillamine.⁶ Trientine may cause haemorrhagic gastritis, ageusia (loss of taste) and rash. Colitis and duodenitis have also been reported with clinical improvement after drug withdrawal. A reversible sideroblastic anaemia has been described in case reports possibly because of the drug's effects on

mitochondrial iron metabolism. The same clinical and laboratory monitoring described for D-penicillamine also applies to trientine.

Zinc salts

Zinc interferes with the uptake of copper from the gastrointestinal tract by inducing enterocyte metallothionein, an endogenous chelator of metals. Experience of zinc in the treatment of WD has largely been for maintenance postchelator therapy but it has been used as primary therapy in patients who developed worsening neurological symptoms with D-penicillamine, during pregnancy and in young children.²¹ Reports of large studies of adults with WD indicate efficacy. Current guidelines, however, recommend that all symptomatic patients with WD should receive a chelating agent.¹⁵

Zinc is dosed according to milligrams of elemental zinc, as different zinc salts (commonly sulfate, acetate and gluconate) are used. The recommended dose is 150 mg elemental zinc/day in three divided doses. Zinc has very few side effects. Gastric irritation is the main problem and may be dependent on the salt prescribed. Hepatic deterioration has been occasionally reported when zinc was given and was fatal in one case.

Adequacy of treatment with zinc is judged by clinical and biochemical improvement and by measuring 24 hours urinary excretion of copper, which should be less than 1.6 μmol per 24 hours on stable treatment.

Future developments

Tetrathiomolybdate is an investigational product with strong decoppering properties.²² Potential adverse effects include bone marrow depression, hepatotoxicity and overly aggressive copper removal, which causes neurological dysfunction. Clinical experience with this drug is limited in patients with WD, and further studies are required.

TRANSPLANTATION

Liver transplantation may be the only option for patients who present with ALF (as occurs in about 5% of patients with WD) and in those with decompensated liver disease who are unresponsive to drug therapy.²³ It should be noted that the term ALF in this situation can be described as a misnomer as most are in fact already cirrhotic, and these patients therefore represent an exception to the standard definition of ALF where those with chronic liver disease are excluded.

Criteria for liver transplant-listing in the UK are established for chronic liver disease with a projected 1 year liver disease mortality without transplantation of >9%, predicted by a United Kingdom Model for End-Stage Liver Disease (UKELD) score of ≥ 49 . The UKELD score is derived from the patient's serum sodium, creatinine and bilirubin and international normalised ratio (INR). For those with advanced liver disease, a prognostic scoring system was proposed and then later revised, taking into account serum bilirubin, white cell count, INR and aspartate aminotransferase (AST). The revised system had a sensitivity, specificity and positive predictive value for determining the need for liver transplantation of 93%, 98% and 88%, respectively.²⁴ It is useful for helping determine the likelihood of transplantation versus successful medical therapy.

Liver transplantation corrects the hepatic metabolic defects of WD and may initiate removal of excess and normalisation of extrahepatic copper. Patients do not require WD-specific treatment post-transplant. Outcomes for liver transplantation for WD are excellent for both those with ALF and chronic liver disease.^{6 25–27}

The role of liver transplantation in neurological predominant WD remains controversial because the liver disease is treatable with medication in most of these patients, and outcomes with liver transplantation are not always beneficial.^{28–31}

ASYMPTOMATIC PATIENTS

For asymptomatic or presymptomatic patients identified through family screening, treatment with a chelating agent, such as D-penicillamine or with zinc, is effective in preventing disease symptoms or progression.

SPECIAL CIRCUMSTANCES

Surgery

Treatment should never be discontinued altogether; patients who stop therapy for WD are at risk for the development of hepatic decompensation and ALF. It is reasonable to reduce the dose of D-penicillamine (and similarly for trientine) prior to surgery since data suggest that it may impair wound healing.

Main messages

- ▶ Wilson disease (WD) should be considered in unexplained liver disease, particularly if there are neuropsychiatric features.
- ▶ Acute liver failure due to WD has high morbidity and mortality rates and is important not to overlook.
- ▶ Treatment exists for all severities of liver disease.
- ▶ Liver transplant is curative for WD but controversial with severe neurological manifestations alone.

Current research questions

- ▶ What is the optimal treatment regimen for Wilson disease?
- ▶ What is the role of new, experimental therapies?

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Pregnancy

Copper status should be optimised prior to pregnancy. Although there is some concern over the teratogenicity of D-penicillamine, the risks of withdrawing treatment outweigh those of continuing it. Interruption of treatment during pregnancy can result in ALF.³²

Acute liver failure (ALF)

A minority of patients with WD will present with ALF. However, it should be remembered that there is underlying advanced fibrosis or cirrhosis in these patients with ALF.¹³ Features seen in these patients include:

- ▶ Coombs-negative haemolytic anaemia.
- ▶ Serum aminotransferases <2000 international unit/L.
- ▶ Ratio of the AST:alanine aminotransferase (ALT) >2.2.
- ▶ Low or normal alkaline phosphatase.
- ▶ Coagulopathy.
- ▶ Rapidly progressive renal failure.
- ▶ KF rings in 50%.

An alkaline phosphatase to bilirubin ratio <4 had a sensitivity of 94%, specificity of 86% and likelihood ratio of 7 for ALF due to WD.¹³ An AST:ALT ratio >2.2 yielded a sensitivity of 94%, a specificity of 86%, and a likelihood ratio of 7 for diagnosing ALF-WD.¹³ Conversely, CP and copper are less sensitive and specific.¹³ Serum copper and 24 hours urinary excretion of copper are usually greatly elevated.

Self-assessment questions

Please answer true or false

1. Patients with acute liver failure secondary to Wilson disease usually do not have any underlying liver disease.
2. The hallmark of Wilson disease is raised serum copper.
3. Neurological worsening after treatment initiation is a common finding.
4. Zinc salts are a good first-line treatment for Wilson disease.
5. Treatment of WD is life-long unless transplanted.

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Answers

1. False
2. False
3. False
4. False
5. True