Wilson's disease

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Abstract

Wilson's disease is a rare progressive genetic disorder of copper metabolism associated with hepatolenticular degeneration. Left untreated, it results in severe disability and death. The diagnosis is very easily overlooked but, if discovered early, effective treatments are available to prevent or reverse many manifestations of this disorder. The role of copper in disease pathogenesis, coupled with clinical, biochemical and genetic markers, is pivotal to establishing a clear diagnosis. Medical therapy involves chelating agents (e.g. penicillamine, trientine) and/or zinc salts. Liver transplantation corrects the underlying pathophysiology and can be life-saving. Knowledge of the Wilson's disease gene has opened up a new molecular diagnostic repertoire in the investigation of suspected patients and first-degree relatives.

Keywords Caeruloplasmin; copper; Kayser–Fleischer rings; liver failure; MRCP; penicillamine; tremor; trientine; Wilson's disease; zinc

Key points

- Wilson's disease (WD) should be considered in individuals with liver abnormalities of uncertain cause and/or new onset movement disorders.
- There is a need for life-long follow-up by specialist units to monitor clinical progress (symptoms, signs, and laboratory tests), to be alert to the side effects of drugs, and to encourage adherence and availability of emerging clinical trials
- Treatment recommendations for WD are in transition with increasing confidence in trientine rather than penicillamine for initial chelation therapy of neurological and hepatic disease. Zinc alone has been advocated for pre-symptomatic/asymptomatic disease, some clinicians still prefer a chelator
- For patients with hepatic WD, treatment can stabilize disease; the outcome of liver transplantation in WD with acute or chronic liver failure untreatable by medical therapy is excellent.

Introduction

Wilson's disease (WD), first described by Kinnier Wilson in 1912, affects between 1:30,000 and 1:100,000 individuals. It is characterized by accumulation of excess copper in the liver caused by reduced excretion of copper in bile. WD is progressive and fatal if not diagnosed and treated (Box 1).

Liver pathology

In early WD, copper is associated with a number of histological changes including macro and macro hepatic steatosis and glycogenated nuclei. Intermediate-stage disease can be indistinguishable from autoimmune hepatitis. Cirrhosis almost invariably follows. In patients with fulminant liver failure, there is often a background of cirrhosis.

Pathogenesis

The gene responsible for WD, *ATP7B* (chromosome 13), is highly expressed in the liver, kidney and placenta. *ATP7B* encodes a transmembrane protein ATPase that functions as a copper-dependent P-type ATPase. Mutations in *ATP7B* can interrupt its normal cellular processing. The most common *ATP7B* mutation of European origin is a substitution of glutamate for histidine at amino acid 1069 (H1069Q).

Diagnosis and course of disease

The clinical range of WD is wide, with acute liver failure or haemolysis (or both), or with chronic liver disease or neurological disease (or both). Most symptoms first appear during the second and third decades of life. Patients presenting with neurological or psychiatric signs tend to be older than those with

Medical treatment recommendations in WD

- Treatment recommendations for WD are in transition. There is increasing confidence in the use of trientine rather than penicillamine for initial chelation therapy of neurological and hepatic disease
- Zinc alone has been advocated for pre-symptomatic and some asymptomatic WD, although some clinicians still prefer a chelator. For maintenance therapy, a reduced dose of chelator or replacement with zinc alone is an option
- There is a need for life-long follow-up by specialist units to monitor clinical progress (symptoms, signs, laboratory tests), to be alert to the adverse effects of drugs, and to encourage compliance
- Clinicians are encouraged in structured monitoring, standardized regimens and assessment, with the publication of outcomes data. Databases (e.g. future international collaborations and registry studies will play an important part in providing these data)
- Patients' associations have an important role in supporting patients and carers

Box 1

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hepatic features alone. Most patients with central nervous system involvement have asymptomatic liver disease.

Hepatic disease

WD can present with fulminant hepatic failure (with Coombs'-negative haemolytic anaemia), renal failure and increased serum/urinary concentrations of copper; approximately 5% of patients present in this manner, usually in the second decade of life. Almost all patients are already cirrhotic.

Serum alkaline phosphatase (ALP) is frequently reduced; a ratio of ALP (IU/litre) to bilirubin (mg/dl) of <2 suggests wilsonian fulminant hepatitis.[1]

In patients presenting with liver disease, neurological features (if they occur) usually become apparent 2–5 years later.

Eye changes

Kayser–Fleischer rings and sunflower cataracts, usually visible only by slit-lamp examination, can be reversed by medical therapy or after liver transplantation. Rings indistinguishable from Kayser–Fleischer rings also occur in chronic liver diseases, long-standing cholestasis and cryptogenic cirrhosis.

Neurological/neuropsychiatric disease

Neurological/neuropsychiatric signs are presenting features in 40–50% of patients. These include an akinetic–rigid syndrome similar to Parkinson's disease, pseudosclerosis (tremor-predominant), ataxia and adystonic syndrome. Behavioural changes, depression, anxiety and frank psychosis are also seen.

Structural brain magnetic resonance imaging (MRI) in patients with WD has shown widespread lesions in the putamen, globus pallidus, caudate, thalamus, midbrain, pons and cerebellum.

Investigations

Apart from genetic analysis, there is no single test for diagnosis. Symptoms are often non-specific, and the disease affects different organ systems, which results in confusion with other disorders. Increasing use of the validated Leipzig scoring could be helpful in helping with diagnosis (Table 1).

The diagnosis is relatively easy to establish in individuals with neurological symptoms, Kayser–Fleischer rings and a low caeruloplasmin concentration. The absence of Kayser–Fleischer rings does not exclude the possibility of WD, but Kayser–Fleischer rings are absent in <2% of patients with predominantly neurological disease.

Genetic studies

The diagnosis is more challenging when liver disease is the presenting feature. Molecular analysis (if available) of *ATP7B* mutations can potentially be diagnostic, but will not necessarily detect all disease-producing mutations.[2]

Caeruloplasmin

A serum caeruloplasmin concentration of <0.2 g/litre (normal range 0.2–0.5 g/litre) is consistent with WD and diagnostic in a patient with Kayser–Fleischer rings. Up to 95% of homozygotic and 20% of asymptomatic heterozygotic patients have serum caeruloplasmin <0.2 g/litre. However, approximately 5% of homozygotes and up to 50% of affected individuals with severe decompensated liver disease have a normal serum caeruloplasmin, presumably because it is an acute-phase reactant.

Leipzig scoring for WD

Typical clinical signs and symptoms	Allocated score per item
Kayser–Fleischer rings	
• Present	2
• Absent	0
Neurological symptoms[a]	
• Severe	2
• Mild	1
• Absent	0
Serum ceruloplasmin	
• Normal (>0.2 g/litre)	0
• 0.1–0.2 g/litre	1
• <0.1 g/litre	2
Coombs-negative haemolytic anaemia	
• Present	1
• Absent	0
Other tests	
Liver copper (in the absence of cholestasis)	
• >5 times ULN (>4 micromol/g)	2
• 0.8–4 micromol/g	1
• Normal (<0.8 micromol/g)	-1
• Rhodamine-positive granules[b]	1
Urinary copper (in the absence of acute hepatitis)	
• Normal	0
• 1–2 times ULN	1
• >2 times ULN	2
• Normal, but five times ULN after penicillamine	3
Mutation analysis	
• Detected on both chromosomes	4
• Detected on one chromosome detected	1
• No mutations detected	0

Evaluation based on total Leipzig score	
Total score	**Evaluation**
Evaluation based on total Leipzig score	
Total score	**Evaluation**
≥4	Diagnosis established
3	Diagnosis possible, more tests needed
≤2	Diagnosis very unlikely

ULN, upper limit of normal.
[a] Or typical abnormalities at brain MRI.
[b] If no quantitative liver copper measurements are available.

Table 1

Hepatic copper

The normal copper content of liver is <55 micrograms/g (dry weight). Accurate analysis requires an adequate sample of liver (>1 cm of a 1.6 mm diameter core). A hepatic copper concentration >250 micrograms/g dry weight is usual in homozygous

WD and (with some caveats) remains the best biochemical test for WD. Diagnosis is sometimes considered retrospectively, after liver biopsy (e.g. from paraffin blocks for quantitative copper measurement). Hepatic copper content is an important indicator of disease, although a value <250 micrograms/g dry weight does not exclude the possibility of disease: extensive fibrosis and few parenchymal cells in the biopsy can result in a copper concentration that is falsely low.

Urinary excretion of copper

Urinary copper is derived from free (non-caeruloplasmin-bound) copper circulating in the plasma. A 24-hours urinary copper excretion >1.6 micromol/24 hours (>100 micrograms/24 hours) is suggestive of WD. Results can be difficult to assess unless wide-necked bottles with copper-free disposable polyethylene liners are used. Urinary copper excretion after penicillamine administration is a useful diagnostic adjunctive test in the paediatric population but is of uncertain value in adults/heterozygote carriers.

Management

There is no universally accepted regimen.[3,4] It is difficult to make definitive recommendations as virtually all the published data have been obtained from clinical series of patients rather than randomized studies. No treatment option is totally effective or reliable.

The drug treatment of WD is based on the use of copper chelators to promote copper excretion, or zinc to reduce copper absorption, or both. Penicillamine is the usual initial treatment, with trientine as an alternative chelator for individuals intolerant of penicillamine. Ammonium tetrathiomolybdate, another chelator, is under assessment in US/European clinical trials for the treatment of neurological WD.

Diet

Chocolate, liver, nuts, mushrooms and shellfish contain high concentrations of copper and are best avoided.

Penicillamine

The British National Formulary suggests 1.5−2 g daily in divided doses, adjusted according to response; maintenance 0.75−1 g daily, a dose of 2 g daily should not be continued for more than one year; maximum 2 g per day.The treatment is best taken 1 hour before or 2 hours after food. The use of lower initial doses, 250−500 mg/day, increasing over weeks, can increase tolerance to the drug.

Regular monitoring of full blood count/urinary protein is recommended. Adverse effects occur in 10−20% of patients and can be severe enough to lead to treatment termination. Early adverse effects (1−3 weeks) include fever, rash, lymphadenopathy, neutropenia, thrombocytopenia and proteinuria; if any of these occur, penicillamine should be stopped and an alternative treatment used. Later adverse effects include nephrotoxicity (a lupus-like syndrome) and bone marrow suppression. Skin complications with long-term use include progeriatric changes, elastosis perforans serpiginosa and aphthous stomatitis. Penicillamine can affect pyridoxine (vitamin B_6) metabolism, and this vitamin should therefore be given (20 mg daily) to at-risk individuals.

In decompensated WD, hepatic function usually improves after therapy. In patients with neurological disease, gradual clinical and cerebral MRI improvement has been documented; in 20−50% of patients with neurological disease, initial neurological deterioration can occur that in some cases cannot be reversed.

Trientine

Trientine is an alternative to penicillamine for initial treatment of WD in those patients who are thought to be intolerant of penicillamine.[5] Trientine chelates copper by forming stable complexes. The initial dose of trientine dihydrochrloride recommended from the European and American guidelines is 1200−1800 mg/day in 2−4 divided doses, taken after food. Maintenance therapy is 900−1200 mg/day (300 mg trientine capsules are equivalent to 200 mg trientine base). Adverse effects include nausea, pancytopenia, hypersensitivity reactions, renal effects, iron deficiency anaemia and severe colitis. Sideroblastic anemia and hepatic siderosis can occur if copper deficiency develops because of excessive treatment. The frequency of neurological deterioration is thought to be less with trientine than with penicillamine. Alternative trientine formulation also include trientine tetrahydrochloride salt.

Zinc

Zinc induces intestinal metallothionein, which binds preferentially to copper within the duodenal enterocyte. Copper absorption is reduced, and copper is lost when the enterocyte is shed during normal cell turnover. Zinc can also induce copper-binding metallothionein in hepatocytes, thereby reducing the damaging effects of free copper. The dosage of zinc for adults is 150 mg/day in elemental form, given in three divided doses. Dyspepsia can be troublesome, and changing the formulation (e.g. zinc acetate) and timing of administration can help.

Zinc has been used successfully in asymptomatic patients. Zinc is as effective as penicillamine in neurological disease. In patients with severe hepatic disease, maintenance therapy with zinc alone is effective after an initial period of treatment with trientine and zinc (given at separate times).

In patients who deteriorate despite therapy or develop fulminant hepatic failure, liver transplantation is available for hepatic disease. However, no such option is available for neurological deterioration; withdrawal of the chelator followed by reintroduction at a lower dosage with gradual escalation can be helpful.

Prognosis

The prognosis for patients with WD is excellent if the disease is diagnosed early and treated appropriately. For patients with hepatic WD, treatment can stabilize disease and even reverse or regress the fibrosis with time. The outcome of liver transplantation in WD with acute or chronic liver failure untreatable by medical therapy is excellent.

Follow-up

Monitoring of medical treatment

Patients on initial therapy should have follow-up appropriate to the severity of their neurological or hepatic features.

During adequate chelation therapy, 24-hours urinary copper should be 3–8 micromol/day (200–500 micrograms). Some experts recommend collection of urine after stopping chelator treatment for 48 hours to assess the urinary copper excretion while off treatment. It is not known which of these approaches is best.

During zinc therapy, 24-hours copper excretion should be <2.0 micromol/day (<125 micrograms). Urinary output of zinc can be measured to show whether sufficient zinc is being taken and absorbed.

During all treatments, an estimation of non-caeruloplasmin-bound (i.e. free) copper is made from the measurements of total copper and caeruloplasmin. The target is a non-caeruloplasmin-bound copper concentration of 50–150 micrograms/litre.

Prevention

Family screening

First-degree relatives must be screened for WD by liver function tests, serum copper and caeruloplasmin concentration, and urinary copper analysis. The probability of finding a homozygote among siblings is 25% and among the children is roughly 0.5%. Molecular genetic analysis is useful for families in whom both mutations have been detected in the index patient. ◆

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