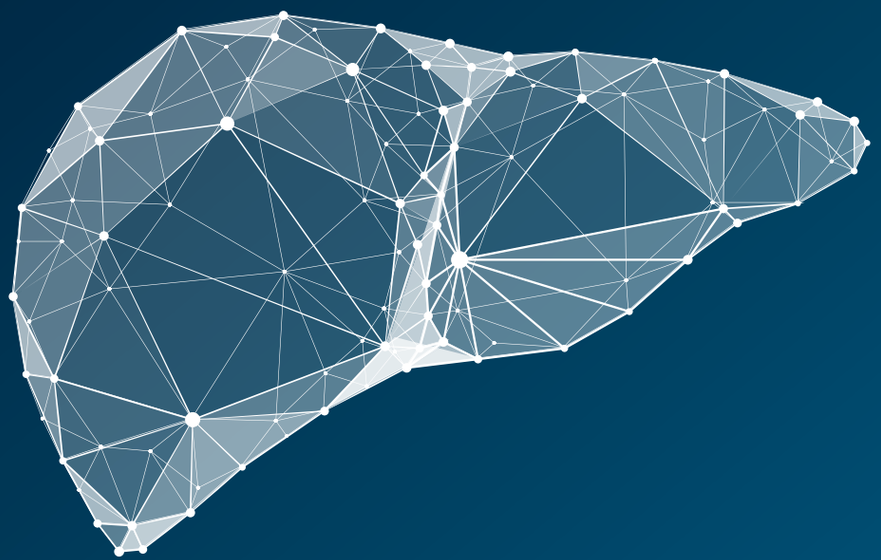
HEPATOLOGY

A clinical textbook

Wedemeyer, Berg, Mauss, Keitel, Rockstroh, Sarrazin

11th Edition **2024**



10. Genetic liver diseases

10.2 Wilson disease

Uta Merle

Abstract

Wilson disease is an autosomal-recessively inherited metabolic disease of the liver. Copper overload leads to organ damage of the liver and other organs. Patients present with either predominant hepatic or predominant neuropsychiatric symptoms, but clinical presentation can vary widely. Manifestation of disease is typically between the ages 5 and 35, but can be also at younger and older ages. In order to diagnose Wilson disease at an early stage and introduce therapy, knowledge of the symptoms and diagnostic criteria is important. Copper overload in Wilson disease patients is treated with either chelating medications (D-penicillamine or trientine) or zinc salts. After introduction of lifelong therapy Wilson disease typically has a favourable disease course and further development of organ-damage can be prevented, especially with respect to liver-damage.

Introduction

Wilson disease is a rare autosomal-recessive disorder of copper metabolism with a prevalence of ~ 1:30, 000. It is not just a disease of children and young adults, but may present at any age. Wilson disease is characterised by hepatic and/or neuropsychiatric symptoms. Clinical presentation can vary widely, but the key features of Wilson disease are liver disease and cirrhosis, neuropsychiatric disturbances and Kayser–Fleischer rings in Desçemet's membrane of the cornea. Without treatment Wilson disease is assumed to be progressive and fatal. Therefore, knowledge of the symptoms, diagnostic criteria and treatment options is important.

Aetiology and pathogenesis

Approximately 50% of dietary copper (~ 0.8 – 2 mg/d) is absorbed in the upper small intestine. After uptake by hepatocytes biliary excretion is the main pathway for elimination of excess copper. In Wilson disease export of copper into bile is impaired leading to a pathological copper accumulation primarily within the liver and subsequently in the brain (particularly in basal ganglia) and other tissues (e.g. kidneys and cornea). Wilson disease is caused by mutations of the Wilson disease gene ATP7B coding for a copper-transporting, transmembrane P-type ATPase primarily expressed in the liver (Bull 1993, Tanzi 1993). About 750 polymorphisms of the ATP7B gene have been described with several of them of to date unknown clinical significance (Czlonkowska 2018). Most Wilson disease patients are compound heterozygotes, possessing alleles with different mutations in both parental genes. The mutation variability has in general no relevant impact on phenotypic expression in individual Wilson disease patients (Ferenci 2019).

In addition to reduced biliary copper excretion impaired ATP7B function leads to a disturbed incorporation of copper into ceruloplasmin. Failure to incorporate copper during ceruloplasmin biosynthesis results in the secretion of an apoprotein that is devoid of enzymatic activity and rapidly degraded. The resulting decrease in serum ceruloplasmin concentration is a diagnostic hallmark of Wilson disease. Because ceruloplasmin accounts for most of serum copper, total serum copper is most often reduced in Wilson disease.

Clinical presentation

Although the biochemical defect that leads to the copper accumulation in Wilson disease is already present at birth, manifestation of Wilson disease is typically between 5 to 35 years of age. Of note, Wilson disease is increasingly diagnosed in children who are less than 5 years-old. Clinical findings may be nonspecific in children who are less than 2 years-old (Wiernicka 2017, Wilson 2000). Although the majority of patients manifest disease-related symptoms until the age of 35, evaluation for Wilson disease should also be carried out in older individuals as manifestation even at higher ages is possible (Ferenci 2007).

Hepatic presentation

Most paediatric patients with Wilson disease present with hepatic disease, whereas adults present with hepatic disease with or without concurrent neuropsychiatric disease. Liver disease associated with Wilson disease can be highly variable. Therefore, Wilson disease is often misdiagnosed, and the average time from symptom onset to diagnostic treatment is long, about 12 months (Merle 2007).

All forms of clinical presentations occur, including clinically asymptomatic states with only biochemical abnormalities, chronic hepatitis, steatosis, splenomegaly, hepatomegaly, and compensated or decompensated liver cirrhosis (Table 1) (EASL Wilson Didease guideline 2012, Schilsky 2022). The features of hepatitis can be similar to other causes of hepatitis, such as chronic viral hepatitis, chronic autoimmune hepatitis, chronic steatohepatitis, or drug-related hepatitis. In some patients transient episodes of hemolysis presenting as intermittent jaundice can occur.

Acute liver failure

About 5% of patients present with a fulminant hepatic failure, typically associated with hemolysis. They have a poor prognosis without liver transplantation. Typically, in these patients cirrhosis is present, although it is the first manifestation of the disease. Diagnosis of Wilson disease presenting as fulminant hepatic failure can be challenging. In these typically young and predominantly female patients coagulopathy, hyperbilirubinaemia, Coombs negative hemolytic anaemia (due to massive release of copper from dying hepatocytes), and elevated serum and urinary copper concentrations as well as often the combination of those are characteristic features. Despite massive hepatic necrosis, which is responsible for the deleterious clinical course especially in the presence of hepatic encephalopathy, serum aminotransferases are usually less than 10 times normal and, thus, much lower than the values commonly recorded in fulminant hepatitis of other etiologies. Renal insufficiency is frequently present but in general reversible. It is a result of tubular injury from copper and of the multi-organ failure that can occur during acute liver failure.

Neuropsychiatric presentation

Neurological symptoms usually develop later than hepatic symptoms, most often in the twenties (Table 1). The initial symptoms may be very subtle, such as changes in behavior, deterioration in practical performances, speech and writing problems with micrographia. Other common findings are tremor, lack of motoric coordination, drooling, dysarthria, dystonia, and spasticity.

Psychiatric abnormalities in Wilson disease patients are more common than generally acknowledged. Approximately 50 to 70% of patients have psychiatric symptoms at the beginning or at later stages of their illness, with or without hepatic or neurological findings (Akil 1991, Mura 2017). These psychiatric symptoms include depression, bipolar disorder, neurotic behaviors, personality changes, anxiety, labile mood, and even frank psychosis (Table 1). Many of the individuals with neuropsychiatric symptoms may have concomitant liver disease that is frequently asymptomatic.

Kayser-Fleischer rings represent the corneal deposition of copper within the Descemet's membrane and have a golden-brown appearance. They are present in nearly all patients with neurological symptoms. About 50% of Wilson disease patients with liver disease lack Kayser-Fleischer rings. In addition, in early stages of the disease and in asymptomatic siblings they are commonly absent.

Other manifestations

In addition to the common hepatic and neuropsychiatric presentations signs and symptoms of Wilson disease may arise as a result of the dysfunction of any organ in which excess copper is deposited. Clinical manifestations may include abnormalities of the kidney (aminoaciduria and nephrolithiasis), the endocrine system (hypoparathyreodism, infertility, secondary amenorrhea, and repeated miscarriages), the heart (cardiac arrhythmias and cardiomyopathy), and the skeleton (premature osteoporosis and arthritis) (Table 1).

Table 1. Clinical symptoms in Wilson disease patients

Manifestation	Clinical symptom
Hepatic	Asymptomatic hepatomegaly
	Isolated splenomegaly
	Acute hepatitis of variable severity
	Chronic hepatitis
	Hepatic steatosis
	Liver cirrhosis, compensated or decompensated
	Acute-on-chronic liver failure
	Acute liver failure, typically with Coombs negative hemolysis, high bilirubin level and high bilirubin:ALP level
Neurological	Dysarthria
	Movement disorders (tremor, involuntary movements)
	Akinetic-rigid syndrome similar to Parkinson's disease
	Gait abnormality, Ataxia
	Dystonia
	Chorea, Athetosis
	Drooling, oropharyngeal dystonia, transfer dysphagia
	Dysautonomia
	Seizures
	Sleep disorder, insomnia
Psychiatric	Depression
	Bipolar spectrum disorder
	Neurotic behaviors
	Personality and behavioral changes
	Psychosis
	Subtle cognitive dysfunction
Eye	Kayser-Fleischer rings, Sunflower cataract

Diagnostic findings

Diagnosis is usually established on the basis of clinical findings and laboratory abnormalities. Based on Sternlieb's criteria diagnosis is straightforward if two or more of the following symptoms are present: Kayser-Fleischer rings, typical neurologic symptoms, low serum ceruloplasmin levels (< 20 mg/dL), and increased hepatic copper content (> 250 µg/g dry weight). Diagnosis is far more complex in patients presenting with liver disease as – compared to patients with primary neurological presentation – diagnostic markers are in ~20% of Wilson disease patients with primary hepatic presentation in the normal range, and by that misleading. In most patients a combination of various parameters is

necessary to firmly establish the diagnosis as no one single finding is adequate for diagnosis of Wilson disease. Not a single test is *per se* specific and, thus, a range of tests has to be applied (Table 2). A diagnostic score based on all available tests was proposed by the Working Party at the 8th International Meeting on Wilson's disease, Leipzig 2001 – commonly named "Leipzig-Score" (Ferenci 2003) (Table 3). The Wilson's disease scoring system provides a good diagnostic accuracy and was re-evaluated also for children with liver disease (Nicastro 2010).

Table 2. Biochemical tests for diagnosis of Wilson disease (adapted to EASL Wilson disease guideline 2012)

Test	Typical finding	False "negative"	False "positive"
Serum ceruloplasmin	Decreased by 50% of lower normal value	"Inflammation, measurement by immunologic assay, pregnancy, contraceptive/ oestrogen therapy"	"Malabsorbtion, protein-losing nephropathy, aceruloplasminaemia, heterozygous carriers, acquired copper deficiency"
24-hour urinary copper	>1.6µmol/24h	Incorrect/incomplete collection, kidney failure	Hepatocellular necrosis, cholestasis, sample contamination, heterozygous carriers
Serum "free" copper	>1.6µmol/L	Normal if ceruloplasmin overestimated by immunological assay	
To date not in clinical routine: Relative exchangeable copper (REC)	>18.5%	Not reported	Not reported
Hepatic copper content	>250µg/g dry weight >4µmol/d dry weight	Sampling error, especially in patients with active liver disease and in patients with regenerative nodules	Cholestatic syndromes
Kayser-Fleischer rings	Present in examination by slit lamp	Absent in up to 50% of Wilson disease patients with hepatic presentation, absent in most asymptomatic siblings	Chronic cholestatic disorders like primary biliary cholestasis

Table 3. Diagnostic criteria for Wilson disease – Leipzig-Score

Kayser-Fleischer ring (slit lamp examination)	
present	2
absent	0
Neurological symptoms and/or typical signs in cMRI	
severe	2
mild	1
absent	0
Serum ceruloplasmin	
Normal (>0.2g/L)	0
0.1-0.2g/L	1
<0.1g/L	2
Coombs negative hemolytic anaemia	
present	1
absent	0
Total liver copper content	
>250µg/g dry weight	2
>50 ≤250µg/g dry weight	1
normal (<50µg/g dry weight)	-1
If no copper-quantification available: positive rhodanine-staining	1
24h-urinary copper excretion	
normal	0
1-2x ULN (upper limit of normal)	1
>2x ULN	2
Normal, but positive D-penicillamine provocation test	2
ATP7B mutation analysis	
present on both chromosomes	4
Present on one chromosome	1
none	0
Total score	**Evaluation**
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

Kayser-Fleischer rings

Kayser-Fleischer rings are found in most neurological Wilson disease patients and in ~ 50% of hepatic patients (Medici 2006, Merle 2007). Although sometimes they can be visible by eye, slit lamp examination is necessary to confirm the presence or absence of Kayser-Fleischer rings.

They are not pathognomonic for Wilson disease, and can also be found in cholestatic liver disease such as primary biliary cirrhosis or intrahepatic cholestasis associated with prolonged parenteral nutrition.

Serum ceruloplasmin

Serum ceruloplasmin is typically decreased below 20 mg/dL in patients with Wilson disease. However, serum ceruloplasmin concentration has its limitations as about 20 to 30% of Wilson disease patients with hepatic symptoms have serum ceruloplasmin levels in the normal range (Steindl 1997). Diagnostic accuracy of serum ceruloplasmin depends on the selected cutoff values (Mak 2008). Serum ceruloplasmin concentrations below 20, 14, and 10 mg/dL showed positive predictive values of 48.3%,

100%, and 100%, respectively, and negative predictive values of 98.7%, 97.1%, and 91.9%. In line with this finding, in the Leipzig score (Ferenci 2003), the informative cutoff is 10 mg/dL. In some Wilson disease patients hormonal and other stimuli can increase the levels of the acute-phase-reactant ceruloplasmin above the lower limit of normal. For example, ceruloplasmin may be elevated in inflammatory stages, during pregnancy, and in response to exogenous administration of oestrogens. Conversely, a reduced serum ceruloplasmin concentration can be seen in about 20% of ATP7B-heterozygotes, in hypoproteinaemia due to renal or enteric protein loss, in severe end-stage liver disease of any aetiology, and in the rare condition of aceruloplasminaemia. Decreased serum ceruloplasmin is in addition reported in patients with non-alcoholic fatty liver disease (NAFLD). In a recent study in NAFLD patients (without diabetes mellitus) a decreased ceruloplasmin ratio (ceruloplasmin value divided by the lower limit of normal) was associated with a more severe histological activity, a diagnosis of Non-alcoholic steatohepatitis, and hepatic iron deposition among patients with NAFLD (Wang 2022).

Total serum copper and relative exchangeable serum copper

In contrast to what would seem intuitive for a disorder of copper overload, total serum copper is often reduced (<70 µg/dL) in Wilson disease due to the lowered level of serum ceruloplasmin. However, serum copper levels vary and can be elevated in the setting of fulminant Wilson disease. The copper that is not part of ceruloplasmin is known as the serum non-ceruloplasmin bound copper concentration and is elevated above 10 µg/dL in most untreated patients. The non-ceruloplasmin bound "free" copper concentration can be calculated using the estimation that approximately 0.3 µg of copper are associated per mg ceruloplasmin:

Serum copper (µg/dL) – 3 x serum ceruloplasmin (mg/dL) = non-ceruloplasmin bound copper (µg/dL)

Recently, the direct exchangeable copper assay has been suggested as a robust and feasible diagnostic tool for Wilson disease. Exchangeable copper corresponds to the labile fraction of copper complexed to albumin and other peptides but not complexed within ceruloplasmin. This exchangeable copper fraction is easily exchanged in the presence of high–copper-affinity chelating agents such as EDTA and can be measured afterwards – and has been proposed as a method for estimating bioavailable non-ceruloplasmin bound copper in the circulation. For diagnostic purposes, the ratio of exchangeable copper to total serum copper, called the "relative exchangeable copper" (REC), with the cutoff set at 18.5%, distinguishes patients with Wilson disease from simple heterozygotes and normal individuals and also from adults and children with various chronic liver diseases (El Balkhi 2011, Guillaud 2018, Poujois 2017, Trocello 2014).

Urinary copper excretion

Urinary copper excretion is commonly increased in patients with Wilson disease and reflects the amount of non-ceruloplasmin copper in the circulation. While a daily urinary copper excretion of 40 µg (0.6 µmol) is the upper limit of normal the conventional level taken as diagnostic of Wilson disease is 100 µg (1.6 µmol). However, urinary copper excretion can also be increased in any disease with extensive hepatocellular necrosis, cirrhosis with cholestasis, and nephrotic syndrome.

Urinary copper excretion after provocation with D-penicillamine may be a utilised as an adjunctive diagnostic test to establish the diagnosis of Wilson disease, but has only been standardised in children (Martins da Costa 1992). Commonly 500 mg of D-penicillamine are administered to untreated patients orally at time zero and 12 h later during a 24-h urine collection and an increase of urinary copper excretion to >1600 µg / 24 hours is considered as diagnostic for Wilson disease.

Liver biopsy

Liver biopsy with determination of hepatic copper content remains the gold standard for diagnosing Wilson disease. Normal hepatic copper content is less than 40 µg/g dry weight and that of Wilson disease patients typically exceeds 250 µg/g dry weight. Lowering the threshold value to 75 µg/g was increases test sensitivity with still acceptable specificity (Ferenci 2005). Another large Chinese study proposed 209 µg/g dry weight as optimal threshold value (with a sensitivity of 99% and specificity of 96% (Yang 2015).

A slightly elevated hepatic copper content can also be associated with cholestatic liver diseases, such as progressive familiar intrahepatic cholestasis type 3 (PFIC 3), primary biliary cirrhosis and primary sclerosing cholangitis (Anheim 2010, Shneider 2011, Sood 2015).

The major problem with hepatic parenchymal copper concentration is that in later stages of Wilson disease the distribution of copper within the liver is often not homogenous. Thus, the concentration can be underestimated due to sampling error. As the accuracy of measurement is improved with adequate specimen size, at least 1-2 cm of biopsy core length should be submitted for copper dry weight analysis (Liggi 2013).

Regarding to liver histology, there is no one single feature pathognomonic for the diagnosis of Wilson disease. Intracellular fat accumulations, hepatitis-like features, Mallory bodies, focal necrosis, fibrosis, and cirrhosis can often be found. The pathology can be similar to an ethanol-induced steatohepatitis, while other patients may show histological signs resembling autoimmune hepatitis. Although histological findings are often not helpful for the diagnosis of Wilson disease, the exclusion of other etiologies by liver biopsy may be equally important. The presence of copper staining in histological sections by rhodanine or by other means can provide supportive evidence for Wilson disease. However, especially in early stages of Wilson disease a negative histochemical staining for copper does not rule out increased hepatic copper content and should not be considered sufficient for the exclusion of Wilson disease. Indeed, hepatic copper concentration can be particularly high under this condition.

Genetic studies

De novo diagnosis by molecular studies remains difficult due to the large number of disease-specific mutations scattered across the coding region ATP7B. Depending on the population tested specific mutations can be prevalent and can facilitate the otherwise cumbersome diagnostic mutation analysis (Ferenci 2006); in northern Europeans, the H1069Q mutation accounts for 60-70% of the disease alleles (Caca 2001, Ferenci 2019, Firneisz 2002, Margarit 2005) and in Asians the A778L mutation occurs in 30% of affected individuals.

Genetic analyses are useful in patients with uncertain diagnosis. In such patients sequencing the ATP7B gene can confirm Wilson disease if two ATP7B mutations are found. Genetic diagnosis of Wilson disease should always be corroborated with clinical and biochemical findings. The absence of two pathogenic mutations does not exclude a diagnosis of Wilson disease.

Other diagnostic tests

By ultrasound imaging signs of liver steatosis or cirrhosis as well as hepato- and splenomegaly can help establishing the diagnosis of Wilson disease.

Magnetic resonance imaging (MRI) of the brain may show increased density on T2 weighed images in the region of the basal ganglia and other regions as well as cortical atrophy. MRI changes are most often seen in Wilson disease patients with neurological manifestation, but may also be found in Wilson disease patients without neurological symptoms or completely asymptomatic patients.

As bone density is frequently decreased in Wilson disease patients performing an osteodensitometry is recommended.

Family screening

Screening should be performed in every first-degree relative of any Wilson disease patient. The probability of finding a homozygote is in siblings 25% and in parents or children 0.5%. There is no one single biochemical test that accurately discriminates between homozygous patients and heterozygote carriers. Kayser-Fleischer rings may be absent at early stages of the disease. Determination of Ceruloplasmin levels and 24-hour urinary copper excretion can be misleading because heterozygotes can have borderline pathological values. The serum ceruloplasmin concentration as a screening tool has poor diagnostic strength due to an inadequate predictive value as a single test. Thus, individuals without Kayser-Fleischer rings who have subnormal ceruloplasmin and abnormal liver functions should undergo a liver biopsy for quantitative copper determination. In first-degree relatives of a patient with two detected mutations, targeted mutational analysis is straightforward as family screening of first-degree relatives. Mutation analysis for screening the family of an index patient with known mutations is by that a very reliable tool. If mutations are not known in the index patient, haplotype analysis may be used (Houwen 1993).

Prognosis

Early diagnosis, correct treatment and compliance with anti-copper treatment are crucial for good prognosis in Wilson disease. This is reflected in studied analysing long-term prognosis: in patients diagnosed early and treated correctly and with good compliance long-term survival in Wilson patients seems to be very similar as for the general population (Bruha 2011). However, Wilson disease patients with liver cirrhosis or primarily neurologic patients diagnosed late or with insufficient treatment compliance show higher mortality compared to healthy controls (Beinhardt 2014, Czlonkowska 2005).

If therapy is started in pre-symptomatic patients, development of symptoms is only rarely seen and prognosis is very good (Walshe 1988). Symptomatic patients in general stabilise or improve on adequate long-term treatment. This is especially true for hepatic symptoms, while neurologic symptoms can persist and sometimes even worsen despite treatment.

Treatment

Medical treatment

Once the diagnosis of Wilson disease is established, lifelong medical treatment is recommended because copper accumulation is progressive and ultimately fatal without specific therapy.

As drug treatment, copper chelating agents and zinc salts are used. Under treatment most Wilson disease patients improve their liver function within 6 to 12 months of treatment. Under sufficient therapy asymptomatic patients (e.g. diagnosed by family screening) should stay asymptomatic. Therapy should be taken lifelong. Discontinuation of medical therapy (e.g. due to incompliance) typically leads to progression of liver disease or of neurological symptoms in 1 to 12 months following treatment discontinuation.

D-penicillamine and trientine are chelating agents that remove copper by enhancing its urinary excretion. Therefore, chelators require adequate renal function to be effective. The mode of action of zinc therapy differs from chelators as zinc inhibits the intestinal uptake of copper by inducing enterocyte metallothionein. Ingested copper is bound to metallothionein in enterocytes and lost via feces due to enterocyte shedding.

In addition to medical de-coppering therapy patients with Wilson disease should avoid intake of

foods and water containing high concentrations of copper.

According to the EASL and the AASLD guidelines on Wilson disease, initial treatment for symptomatic patients should include a chelating agent (EASL Wilson disease guideline 2012, Schilsky 2022). Although the larger body of published evidence exists for penicillamine, trientine seems to have a more favourable safety profile, especially in patients with neurological symptoms. Treatment of pre-symptomatic patients and lifelong maintenance therapy of successfully treated symptomatic patients can be accomplished with zinc salts or chelating agents in a reduced dosage. Nevertheless, definitive recommendations are difficult as randomised head-to-head studies are missing.

D-penicillamine

D-penicillamine was introduced 1956 as the first oral treatment for Wilson disease. Besides its action as a copper chelator it may be able to induce hepatic metallothionein synthesis which is capable of sequestering copper in a non-toxic form within cells (Scheinberg 1987). There is a large body of published evidence that D-penicillamine can effectively ameliorate hepatic and neurological symptoms. In addition, it can prevent the onset of disease in asymptomatic patients detected by family screening.

The usual dosage of D-penicillamine for initial treatment is 900 – 1, 800 mg/day divided in 2 to 4 dosages. For maintenance treatment a reduced dose of 600 – 900 mg/day is recommended. Because absorption can be impaired if taken with a meal D-penicillamine should be taken 1h before or 2h after a meal.

The disadvantage of D-penicillamine is its serious toxicity with a side-effects rate of 25 – 30%. These adverse events can be divided in short- and long-term adverse effects. In the first 1 to 3 weeks after starting D-penicillamine therapy hypersensitivity reactions like rash, fever, neutropenia, thrombocytopenia, proteinuria, and lymphadenopathy can occur. These early side effects may be managed by stopping D-penicillamine treatment and using an alternative drug. An early serious side-effect is neurological worsening that is seen especially in patients with a neurological presentation or at least pre-existing neurological symptoms (Litwin 2015). Neurological worsening recovers only in about half of the patients. Immunologically induced long-term effects require immediate cessation of D-penicillamine treatment. They include systemic lupus erythematodes, immune complex nephritis, Goodpasture syndrome, arthritis, and bone marrow depression with leucopenia and thrombocytopenia. Long-term effects that are dose-dependent and due to interference with collagen and elastin formation include skin lesions like cutis laxa and elastosis perforans serpingiosa.

Triethylentetramine / Trientine

Trientine (Triethylentetramine) is a chelating drug that was introduced in 1969 as an alternative to D-penicillamine. Trientine exists as two different salts: Triethylentetramine/trientine dihydrochloride (TETA-2HCl) and Triethylentetramine/trientine tetrahydrochloride (TETA-4HCl). Both salt formulations are stable and can be stored at room temperature.

Trientine is effective by promoting renal copper excretion like D-penicillamine does but seems to have fewer side-effects. In addition, accumulated clinical experience suggests that adverse effects due to D-penicillamine resolve when trientine is substituted for D-penicillamine and do not recur. Especially the initial neurological worsening is thought to be less frequent than under D-penicillamine treatment – although head-to-head comparison was never performed. Reported side effects are few and include iron deficiency anaemia. Rarely seen side-effects are colitis and pancytopenia.

Trientine is an effective treatment and is indicated especially in patients who are intolerant to D-penicillamine. As trientine formulations are typically more cost-expensive than D-penicillamine, notion should be given to decision taken by national health authorities concerning reimbursement.

Dose is referred to mg of trientine-base. Adult dose for trientine-2HCl is 800 to 1600 mg/day (4–8 capsules á 200mg trientine-base) and for trientine-4HCl is 450 to 975 mg/day (3 to 6½ tablets á 150mg trientine-base). Because absorption can be impaired by parallel intake of food trientine should be administered 1 h before or 2 h after meals, in two or three divided doses. As for D-penicillamine, for maintenance therapy trientine-dose can be reduced to a lower dosage than necessary in the initial phase.

When switching from one trientine-salt formulation to the other the higher bioavailability of trientine-4HCl than trientine-2HCl should be taken into account (Weiss 2021). Approximately 0.6mg of trientine base (of 4HCl formulation) equates to 1mg of trientine-base (of the 2HCl formulation). Subsequently, dosage is titrated according to clinical response and urinary copper excretion.

Zinc salts

Zinc salts were first used as treatment for Wilson disease in the early 1960s. In contrast to chelating agents zinc blocks copper absorption in the gastrointestinal tract by inducing metallothionein synthesis in enterocytes. Copper is bound to metallothionein with a high affinity and subsequently is lost when enterocytes shed during normal cell turnover. The dose of elemental zinc is 150 mg per day, given in three doses. Effectiveness of treatment is dependent on the strict administration separately from meals, because food and even milk can interfere with zinc absorption. A major advantage of zinc therapy is its safety with no serious side-effects reported (Brewer 1997, Hoogenraad 1987). The frequently occurring zinc-related dyspepsia can sometimes be overcome by changing the zinc formulation (to acetate, sulphate, or gluconate), but sometimes may cause the need for a change to another treatment.

Treatment failures under zinc-therapy can occur. Therefore, patients under zinc therapy should be followed regularly.

Tetrathiomolybdate

Tetrathiomolybdate is another chelating agent which complexes protein-bound copper. When taken together with meals, it complexes copper in the food and prevents its absorption. Taken separately from foods, tetrathiomolybdate is absorbed and complexes copper with albumin rendering it unavailable for cellular uptake. Tetrathiomolybdate as the more stable bis-choline salt of the drug is in late stages of drug development – but is not yet commercially available. Data from phase II suggested that tetrathiomolybdate caused an effective reduction in non-ceruloplasmin bound copper and an improvement in clinical neurological symptoms. It appears to be useful for the initial treatment of neurological patients. However, tetrathiomolybdate has not yet been released by the authorities for general clinical use and trials continue to determine if more chronic use may be effective and tolerated.

Treatment has to be monitored to ensure its efficacy and the compliance with treatment, and to identify adverse events. Patients should be monitored at least twice a year. Especially shortly after starting treatment a frequent monitoring is recommended. To confirm the clinical and biochemical improvement liver function tests and neurological assessment should be performed.

Monitoring of treatment

For routine monitoring, serum copper and ceruloplasmin, liver enzymes and international normalised ratio, functional parameters, complete blood count and urine analysis as well as physical and neurological examinations should be performed regularly, at least twice annually (EASL Wilson disease guideline 2012). More frequent monitoring is required in the initial phase after diagnosis and initiation of treatment, if symptoms worsen and if nonadherence to treatment is suspected.

Adequacy of chelating treatment can best be assessed by measuring 24-h urinary copper excretion. The 24-hour urinary copper excretion on medication and after 2 days of cessation of therapy should be measured at least yearly (EASL Wilson disease guideline 2012). An adequate long-term treatment can be postulated if the 24-h urinary copper excretion (measured after two days of treatment cessation) is below 100 µg/d (1.6 µmol/d). Urinary copper excretion upon initiation of treatment is often 1000–2000µg/24 h (16-32µmol/L) (for D-penicillamine) and >1000 µg/24 h (8µmol/L) (for trientine) and decreases over time on treatment. With chronic (maintenance) treatment, urinary copper excretion should be for D-penicillamine and trientine approximately 150–500 µg/24 h (3–8 µmol/24 h) (Pfeiffenberger 2019).

For monitoring zinc-therapy collection of 24-h urine under zinc treatment is recommended. Efficiency of zinc treatment can be supposed if 24-h urinary copper excretion is below 100 µg/d (1.6 µmol/d), while compliance with zinc therapy and adequate absorption of zinc is reflected in a 24-h urinary zinc excretion of more than 2 mg/d.

In addition, the efficiency of therapy can be estimated from the non-ceruloplasmin bound copper concentration in serum that should be below 10 µg/dL (<1.6 µmol/L).

Liver transplantation

Liver transplantation corrects the underlying metabolic defect and by that cures the disease. However, the great shortage of donor organs and the need for immunosuppression posttransplantation render liver transplantation only an option in fulminant Wilson disease or in patients especially with decompensated liver disease unresponsive to medical therapy. The outcome of liver transplantation is excellent with one-year survival rates of 80% to 90%. Neurological symptoms can improve after liver transplantation (Weiss 2013), but the outcome of patients with neurological symptoms is inferior to patients without. Thus, the indication for liver transplantation in patients with neurological symptoms should be evaluated carefully.

Key messages

- Wilson disease should be considered in any individual with liver abnormalities or neuropsychiatric symptoms of uncertain cause. Although the disease typically manifests between 5 to 35 years, age alone should not be the basis for excluding Wilson disease.
- Recognition and diagnosis of Wilson disease at an early stage has an impact on prognosis.
- Diagnostic gold standard is hepatic copper content (measured in dry weight). In untreated patients, normal hepatic copper content excludes a diagnosis of Wilson disease with high certainty.
- Genetic diagnosis of Wilson disease should always be corroborated with clinical and biochemical findings. The absence of two pathogenic mutations does not exclude a diagnosis of Wilson disease.
- Initial treatment for symptomatic patients with Wilson disease should include a chelating agent (D-penicillamine or trientine).
- Treatment is lifelong and should not be discontinued, unless liver transplantation is performed.
- Patients should adhere to medical therapy and to a diet avoiding foods and water with high concentrations of copper.
- Routine monitoring should be performed regularly, at least twice annually.

Future directions

For approximately ten years, there has been a rapid improvement in the efficiency of procedures of genetic analysis. As a consequence of improvements and greater availability of genetic testing, a relevant part of patients with and also without suspicion of Wilson disease will receive a test report stating that an ATP7B-variant of unknown significance has been detected. As medical therapy of Wilson disease is recommended also in asymptomatic patients, it will be of even increasing relevance to classify ATP7B variants for their clinical effects thoroughly. This is especially important, as Wilson disease is among a limited number of inherited diseases for which symptoms can be prevented if the affected individuals can be identified and intervened early.

With respect to future therapies currently two gene therapy studies are ongoing in Wilson disease patients. Both constructs (UX701 from Ultragenyx Pharmaceutical and VTX-801 from Vivet Therapeutics) are based on adeno-associated viral vectors and contain a shortened form of the ATP7B gene, which is otherwise too large to package in an adeno-associated viral vector.

Both studies use single intravenous application of the investigational drug. Patients with Wilson disease and clinicians are eagerly awaiting the results of these ongoing clinical gene therapy trials. The ongoing trials will demonstrate if the correction of copper metabolism is only temporary or long term at the point that anti-copper medications can be stopped, offering a real life-changing solution to patients.

References

Akil M, Schwartz JA, Dutchak D, Yuzbasiyan-Gurkan V, and Brewer GJ. The psychiatric presentations of Wilson's disease, J Neuropsychiatry Clin Neurosci. 1991;3:377-382.

Anheim M, Chamouard P, Rudolf G, et al. Unexpected combination of inherited chorea-acanthocytosis with MDR3 (ABCB4) defect mimicking Wilson's disease, Clin Genet. 2010;78:294-295.

Beinhardt S, Leiss W, Stattermayer AF, et al. Long-term outcomes of patients with Wilson disease in a large Austrian cohort, Clin Gastroenterol Hepatol. 2014;12:683-689.

Brewer GJ, Johnson V, and Kaplan J. Treatment of Wilson's disease with zinc: XIV. Studies of the effect of zinc on lymphocyte function, J Lab Clin Med. 1997;129:649-652.

Bruha R, Marecek Z, Pospisilova L, et al. Long-term follow-up of Wilson disease: natural history, treatment, mutations analysis and phenotypic correlation, Liver Int. 2011;31:83-91.

Bull PC, Thomas GR, Rommens JM, Forbes JR, and Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene, Nat Genet. 1993;5:327-337.

Caca K, Ferenci P, Kuhn HJ, et al. High prevalence of the H1069Q mutation in East German patients with Wilson disease: rapid detection of mutations by limited sequencing and phenotype-genotype analysis, J Hepatol. 2001;35:575-581.

Czlonkowska A, Litwin T, Dusek P, et al. Wilson disease, Nat Rev Dis Primers. 2018;4:21.

Czlonkowska A, Tarnacka B, Litwin T, Gajda J, and Rodo M. Wilson's disease-cause of mortality in 164 patients during 1992-2003 observation period, J Neurol. 2005;252:698-703.

El Balkhi S, Trocello JM, Poupon J, et al. Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis, Clin Chim Acta. 2011;412:2254-2260.

European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease, J Hepatol. 2012;56:671-685.

Ferenci P. Regional distribution of mutations of the ATP7B gene in patients with Wilson disease: impact on genetic testing, Hum Genet. 2006;120:151-159.

Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease, Liver Int. 2003;23:139-142.

Ferenci P, Czlonkowska A, Merle U, et al. Late-onset Wilson's disease, Gastroenterology. 2007;132:1294-1298.

Ferenci P, Steindl-Munda P, Vogel W, et al. Diagnostic value of quantitative hepatic copper determination in patients with Wilson's Disease, Clin Gastroenterol Hepatol. 2005;3:811-818.

Ferenci P, Stremmel W, Czlonkowska A, et al. Age and Sex but Not ATP7B Genotype Effectively Influence the Clinical Phenotype of Wilson Disease, Hepatology. 2019;69:1464-1476.

Firneisz G, Lakatos PL, Szalay F, et al. Common mutations of ATP7B in Wilson disease patients from Hungary, Am J Med Genet. 2002;108:23-28.

Guillaud O, Brunet AS, Mallet I, et al. Relative exchangeable copper: A valuable tool for the diagnosis of Wilson disease, Liver Int. 2018;38:350-357.

Hoogenraad TU, Van Hattum J, and Van den Hamer CJ. Management of Wilson's disease with zinc sulphate. Experience in a series of 27 patients, J Neurol Sci. 1987;77:137-146.

Houwen RH, Roberts EA, Thomas GR, and Cox DW. DNA markers for the diagnosis of Wilson disease, J Hepatol. 1993;17:269-276.

Liggi M, Mais C, Demurtas M, et al. Uneven distribution of hepatic copper concentration and diagnostic value of double-sample biopsy in Wilson's disease, Scand J Gastroenterol. 2013;48:1452-1458.

Litwin T, Dziezyc K, Karlinski M, et al. Early neurological worsening in patients with Wilson's disease, J Neurol Sci. 2015;355:162-167.

Mak CM, Lam CW, and Tam S. Diagnostic accuracy of serum ceruloplasmin in Wilson disease: determination of sensitivity and specificity by ROC curve analysis among ATP7B-genotyped subjects, Clin Chem. 2008;54:1356-1362.

Margarit E, Bach V, Gomez D, et al. Mutation analysis of Wilson disease in the Spanish population -- identification of a prevalent substitution and eight novel mutations in the ATP7B gene, Clin Genet. 2005;68:61-68.

Martins da Costa C, Baldwin D, Portmann B, et al. Value of urinary copper excretion after penicillamine challenge in the diagnosis of Wilson's disease, Hepatology. 1992;15:609-615.

Medici V, Trevisan CP, D'Inca R, et al. Diagnosis and management of Wilson's disease: results of a single centre experience, J Clin Gastroenterol. 2006;40:936-941.

Merle U, Schaefer M, Ferenci P, and Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study, Gut. 2007;56:115-120.

Mura G, Zimbrean PC, Demelia L, and Carta MG. Psychiatric comorbidity in Wilson's disease, Int Rev Psychiatry. 2017;29:445-462.

Nicastro E, Ranucci G, Vajro P, Vegnente A, and Iorio R. Re-evaluation of the diagnostic criteria for Wilson disease in children with mild liver disease, Hepatology. 2010;52:1948-1956.

Pfeiffenberger J, Lohse CM, Gotthardt D, et al. Long-term evaluation of urinary copper excretion and non-caeruloplasmin associated copper in Wilson disease patients under medical treatment, J Inherit Metab Dis. 2019;42:371-380.

Poujois A, Trocello JM, Djebrani-Oussedik N, et al. Exchangeable copper: a reflection of the neurological severity in Wilson's disease, Eur J Neurol. 2017;24:154-160.

Scheinberg IH, Sternlieb I, Schilsky M, and Stockert RJ. Penicillamine may detoxify copper in Wilson's disease, Lancet. 1987;2:95.

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.

Shneider BL. ABCB4 Disease Presenting with Cirrhosis and Copper Overload-Potential Confusion with Wilson Disease, J Clin Exp Hepatol. 2011;1:115-117.

Sood V, Rawat D, Khanna R, and Alam S. Cholestatic liver disease masquerading as Wilson disease, Indian J Gastroenterol. 2015;34:174-177.

Steindl P, Ferenci P, Dienes HP, et al. Wilson's disease in patients presenting with liver disease: a diagnostic challenge, Gastroenterology. 1997;113:212-218.

Tanzi RE, Petrukhin K, Chernov I, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene, Nat Genet. 1993;5:344-350.

Trocello JM, El Balkhi S, Woimant F, et al. Relative exchangeable copper: a promising tool for family screening in Wilson disease, Mov Disord. 2014;29:558-562.

Walshe JM. Diagnosis and treatment of presymptomatic Wilson's disease, Lancet. 1988;2:435-437.

Wang Q, Zhou D, Wang M, et al. A Novel Non-Invasive Approach Based on Serum Ceruloplasmin for Identifying Non-Alcoholic Steatohepatitis Patients in the Non-Diabetic Population, Front Med (Lausanne). 2022;9:900794.

Weiss KH, Schafer M, Gotthardt DN, et al. Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease, Clin Transplant. 2013;27:914-922.

Weiss KH, Thompson C, Dogterom P, et al. Comparison of the Pharmacokinetic Profiles of Trientine Tetrahydrochloride and Trientine Dihydrochloride in Healthy Subjects, Eur J Drug Metab Pharmacokinet. 2021;46:665-675.

Wiernicka A, Dadalski M, Janczyk W, et al. Early Onset of Wilson Disease: Diagnostic Challenges, J Pediatr Gastroenterol Nutr. 2017;65:555-560.

Wilson DC, Phillips MJ, Cox DW, and Roberts EA. Severe hepatic Wilson's disease in preschool-aged children, J Pediatr. 2000;137:719-722.

Yang X, Tang XP, Zhang YH, et al. Prospective evaluation of the diagnostic accuracy of hepatic copper content, as determined using the entire core of a liver biopsy sample, Hepatology. 2015;62:1731-1741.