

Wilson disease in children and young adults - State of the art

Atchariya Chanpong^{1,2}, Anil Dhawan¹

¹Paediatric Liver, GI and Nutrition Centre, MowatLabs, King's College Hospital, Denmark Hill, London, United Kingdom, ²Division of Gastroenterology and Hepatology, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

Abstract

Wilson disease (WD) is an autosomal recessive disorder caused by mutations of the *ATP7B* gene, with a reported prevalence of 1:30,000–50,000. *ATP7B* encodes an enzyme called transmembrane copper-transporting ATPase, which is essential for copper incorporation into ceruloplasmin and for copper excretion into the bile. A lack or dysfunction of this enzyme results in a progressive accumulation of copper in several organs, especially in the liver, the nervous system, corneas, kidneys, and heart. Children with WD can present with asymptomatic liver disease, cirrhosis, or acute liver failure, with or without neurological and psychiatric symptoms. Approximately 20%–30% of WD patients present with ALF, while most of the other patients have chronic progressive hepatitis or cirrhosis if untreated. Although genetic testing has become a more important diagnostic tool for WD, the diagnosis remains based on both clinical features and laboratory investigations. The aims of treatment are to reduce copper levels and prevent its accumulation in the liver and other organs, especially in the central nervous system. Liver transplantation in WD is a life-saving option for patients presenting with liver failure and encephalopathy. For WD patients treated with chelating agents, adherence to the therapy is essential for long-term success. In this review, we also address specific issues in young adults as compared to children.

Keywords: Acute hepatic decompensation, chelating agents, chronic liver disease, copper metabolism, fulminant hepatic failure, liver transplantation, Wilson disease

Address for correspondence: Prof. Anil Dhawan, Paediatric Liver, GI and Nutrition Centre, MowatLabs, King's College Hospital, Denmark Hill, London SE5 9RH, UK.

E-mail: Anil.dhawan@nhs.net

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INTRODUCTION

Wilson disease (WD) is an autosomal recessive disorder caused by mutations of the *ATP7B* gene, with a reported prevalence of 1:30,000–50,000.^[1-5] *ATP7B* encodes an enzyme called transmembrane copper-transporting ATPase, which is essential for copper incorporation into ceruloplasmin and for copper excretion into the bile [Figure 1]. A lack or dysfunction of this enzyme results in a progressive accumulation of copper in several organs, especially in the liver, the nervous system, corneas,

kidneys, and heart. Children with WD can present with asymptomatic liver disease, cirrhosis, or acute liver failure (ALF), with or without neurological and psychiatric symptoms.^[1] Approximately 20%–30% of WD patients present with ALF, while most other patients have chronic progressive hepatitis or cirrhosis if untreated.^[6]

PATHOPHYSIOLOGY


a. Genetics

The common mutations of the *ATP7B* gene located on chromosome 13 are missense and nonsense and can

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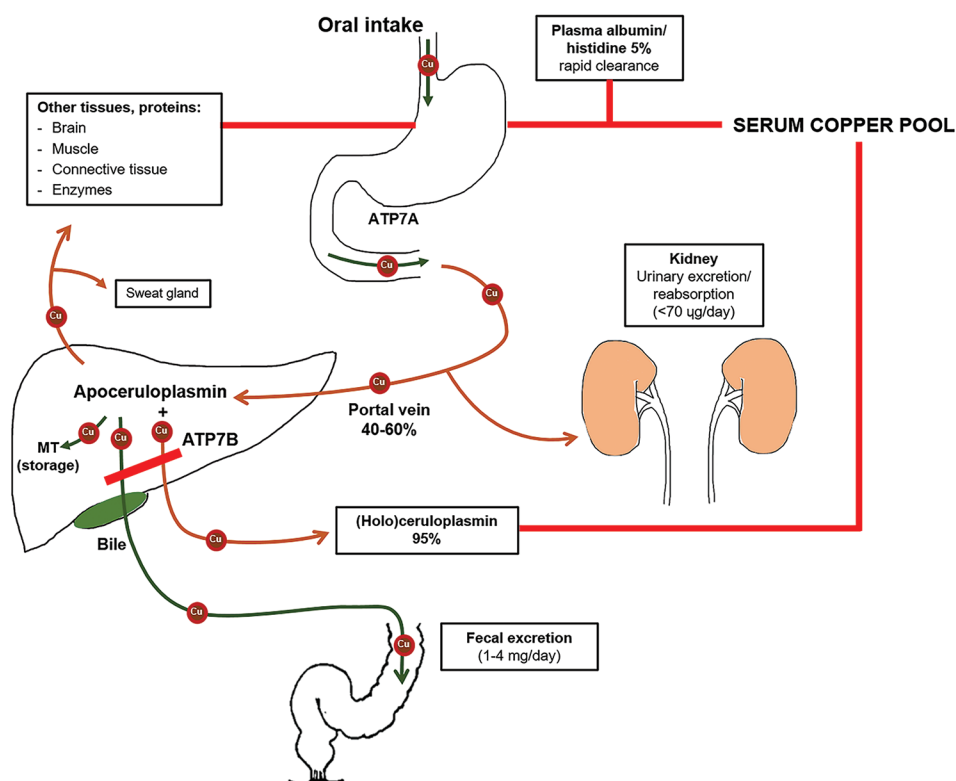


Figure 1: Human copper metabolism

be either homozygous for one mutation or compound heterozygous (two different disease-causing mutations). Although more than 700 mutations have been found to cause WD, missense mutation H1069Q is the most prevalent one (50%–80%) in the European and American population,^[7,8] while mutation R778L is more common (14%–49%) in Far East Asian countries.^[9,10]

Several studies^[11-16] demonstrated that different *ATP7B* variants lead to different disease phenotypes. Patients with homozygous H1069Q mutation frequently present with neurological symptoms, but at a later onset than compound heterozygous ones.^[12,13] While patients with truncating mutations often present with ALF,^[15] there is a lack of definite genotype/phenotype correlation in WD, suggesting the potential role of epigenetics from environmental and nutritional factors on WD phenotypes.^[17]

b. Copper metabolism and homeostasis in hepatocytes

Copper is an essential trace element, especially for mitochondrial respiration. It is absorbed from food into the body through intestinal mucosa by using ATP7A transporter and transported via the portal system to the liver. A minority is excreted via urine and sweat [Figure 1].

Copper enters hepatocytes through copper transporter1 (CTR1) to reach the trans-Golgi network via ATP7B. Following

that, copper incorporates into apoceruloplasmin (half-life: 5 h) to form holoceruloplasmin (half-life: 5 days) and excretes into the circulation.^[18] Of note, holoceruloplasmin is the major copper-containing protein with six copper atoms per molecule. ATP7B also facilitates copper excretion into the bile by forming vesicles that traffic to the biliary canaliculi and excreted in stool [Figure 2].

Mutations of the *ATP7B* gene result in the reduction of levels of ATP7B encoding protein and an increase in the protein degradation, leading to toxic accumulation of copper in the liver and subsequently to an excess of non-ceruloplasmin-bound copper in the bloodstream [Figure 2]. The excess copper is also taken up by other tissues (e.g, brain, eyes, and heart) via CTR1 and divalent metal transporter (DMT) even when in excess intracellularly. Cellular copper overload leads to oxidative stress and subsequent oxidative damage to cellular proteins, lipids, DNA, RNA, and mitochondria.^[17]

Hepatic injury is the most common presentation in children with WD, as liver is the major organ responsible for copper homeostasis.^[17] Initially, copper binds with metallothionein (MT), intracellular proteins that play an important role in metal homeostasis (storage and detoxification). This binding can be detected

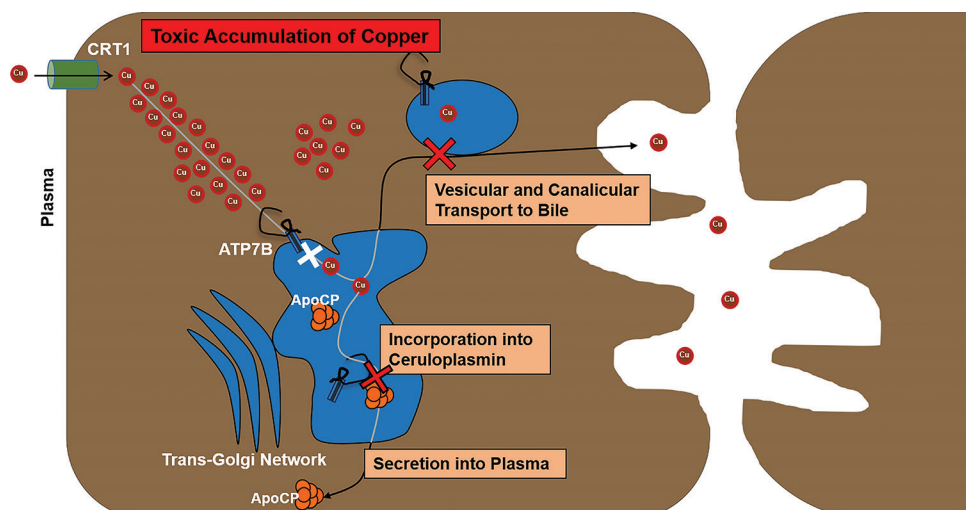


Figure 2: Copper homeostasis in the hepatocytes and canalicular membrane

with special staining (rhodanine and orcein) on liver histology.^[19] With time, copper accumulates in lysosomes and progressively causes mitochondrial damage leading to hepatic steatosis, hepatitis, fibrosis, and macronodular cirrhosis.

Subsequently, non-ceruloplasmin-bound excess and toxic copper leaks into the blood and accumulates in the other tissues. In the brain, chronic toxicity of copper leads to demyelination, damaged astrocytes, and tissue disintegration, particularly in the basal ganglia, thalamus, cerebellum, and brainstem.^[17,20]

In the bloodstream, a rapid increase of free copper causes oxidative damage of hemoglobin and cell membrane, resulting in Coombs-negative hemolysis.^[21] In the muscle, copper induces the inhibition of Na^+/K^+ -ATPase activity, leading to rhabdomyolysis.^[22] Similarly, in the kidney, excess copper can cause renal tubulopathy.^[20]

CLINICAL PRESENTATIONS

WD in children may present at any age with the reported median age of 13 years^[20,23]; however, symptomatic disease is uncommon before the age of 3 years.^[20,24] Hepatic manifestations are more common in children, although some (4%–6%) could present with subtle neurological symptoms. It is more common for older children and young adults (aged 20–30 years) to manifest with neurological or psychiatric symptoms, with or without liver involvement.^[1,17]

a. Hepatic manifestations

Hepatic manifestations vary from asymptomatic or incidental findings of abnormal liver tests, complications of chronic liver disease, to ALF.^[1] At early stage, patients

may be asymptomatic but may be accidentally found with an elevated liver enzyme or abnormal findings on liver ultrasound. Once the disease progresses, patients may present with signs and symptoms of chronic liver disease (e.g., hepatosplenomegaly), or complications from cirrhosis (e.g., ascites and variceal bleeding). WD should always be in the differential diagnosis for any child or young adult presenting with abnormal liver tests or with clinical features of non-alcoholic fatty liver disease or autoimmune liver disease.^[25,26]

ALF-like presentation is a severe form of WD characterized by jaundice, hepatitis, hepatomegaly, and coagulopathy, with or without encephalopathy in previously well children. The Pediatric Acute Liver Failure (PALF) study group suggests the definition of ALF as an INR of ≥ 1.5 in the presence of encephalopathy or an INR of ≥ 2.0 regardless of the encephalopathy.^[27] Some children may have a past history of acute self-limited hepatitis-like illness, recurrent jaundice, hemolytic anemia, or elevated transaminases.^[17] Some clinicians consider this presentation as acute-on-chronic liver failure, as invariably there is evidence of preexisting chronic liver damage on liver histology. Acute on chronic liver failure (ACLF) is defined in patients with an acute hepatitis insult that causes jaundice (total serum bilirubin >5 mg/dL or $85 \mu\text{mol/L}$) and coagulopathy (INR >1.5), together with ascites and/or hepatic encephalopathy within 4 weeks.^[28]

The differentiating features of WD from other causes of hepatic failure are the relatively milder elevation of the liver enzymes (AST/ALT), high total bilirubin, and low alkaline phosphatase.^[17,20,29] Associated hemolysis due to free copper could lead to a high total bilirubin.

b. Neurological manifestation

Neuropsychiatric symptoms are rarely seen in children, especially in those younger than 10 years; however, 5%–15% of children with hepatic manifestations could also have neurological symptoms.^[17,30] These symptoms include incoordination (e.g., handwriting deterioration - dysgraphia), declining performance at school, mild cognitive impairment such as working memory, language difficulties (dyslalia), or movement disorders (e.g., tremor). Psychiatric symptoms can vary from behavioral and personality problems (aggressive and impulsive), mood disorders (depression, anxiety, and bipolar), to psychosis.

Although brain MRI provides variable diagnostic yields, it has become an important diagnostic tool for patients presenting with neurological signs/symptoms. It could also be used for monitoring as some findings may reverse during copper-chelating therapy. Common findings in WD include hyperactive intensity lesions visualized on T2-weighted images located in the basal ganglia (particularly putamen and caudate nuclei), thalamus, midbrain, and pontine white matter.^[31,32] These findings suggest cerebral involvement in WD. Conversely, high-signal intensity lesions in the basal ganglia on T1-weighted images can be secondary to chronic liver disease and hence may indicate WD with hepatic involvement.^[17,20]

Other extrahepatic manifestations are shown in Table 1.

DIAGNOSIS

Clinical manifestations of WD are varied and other causes of liver disease can mimic WD. Therefore, the diagnosis is based on both clinical features and laboratory investigations.

In 2001, a WD diagnostic score [Table 2] was developed by the Working Group at the 8th International Meeting on Wilson's disease in Leipzig.^[35] By providing good accuracy for the diagnosis of WD, this score has been widely used and subsequently incorporated into the diagnostic algorithm in the European Association for the Study of the Liver (EASL) guidelines.^[36] A further validation with children and young adults by Koppikar and Dhawan also demonstrated a high diagnostic value of the score.^[37]

a. Serum copper and exchangeable copper (CuEXC) determination

Total serum copper, which includes those incorporated in ceruloplasmin (holoceruloplasmin), in WD patients is typically low due to poor incorporation of copper into

apoceruloplasmin. However, the level can be normal or high irrespective of the level of ceruloplasmin; this indicates a sudden release of free copper from the liver to the bloodstream, so-called non-ceruloplasmin-bound copper (NCC). The amount of NCC is relatively calculated from total serum copper and ceruloplasmin concentrations with the following equation^[38]:

$$\text{NCC } (\mu\text{g/L}) = \text{Serum copper } (\mu\text{g/L}) - [3.15 \mu\text{g/mg ceruloplasmin} \times \text{ceruloplasmin (mg/L)}]$$

The concentration of NCC in WD is more than 200 mg/L, or even higher (up to 10 times) in WD presented with ALF or hemolysis, whereas the level in normal individuals is approximately 50–100 mg/L. It is worth noting that the drawback of this calculation is that it depends highly on the accurate estimations of serum copper and ceruloplasmin levels.

A new promising test, namely, exchangeable copper (CuEXC), has been developed to specifically measure plasma unbound copper, independent of the level of ceruloplasmin. The normal level of CuEXC is 0.62–1.15 $\mu\text{mol/L}$; the values above this range indicate copper overload in the tissue and bloodstream. A cut-off of 2.08 $\mu\text{mol/L}$ is associated with the presence of extrahepatic manifestations.^[39] However, the availability of this test is limited given its high analytic cost; therefore, it is mainly used in research facilities.

Relative exchangeable copper (REC) is the ratio between CuEXC and total serum copper, representing the toxic blood copper fraction. A value of >18.5% could help diagnose WD with 100% sensitivity and specificity.^[39-41]

b. Urinary copper and penicillamine challenge test

As the excess copper is excreted in the urine, urinary copper has been utilized as one of the diagnostic tools for WD diagnosis. It should be noted that the accuracy of urinary copper concentration is likely dependent on the careful collection timing, type of container, and laboratory expertise.

For baseline 24-h urinary copper, a cut-off of 0.64–1.60 $\mu\text{mol/24 h}$ has been used, given it provides a sensitivity of 50%–80% and a specificity of 75.6%–98.3%.^[42] The level can be <1.6 $\mu\text{mol/24 h}$ at presentation, especially in asymptomatic patients or those with mild liver disease (accounted for 16%–23% of WD patients).^[43] Despite that, the interpretation of 24-h urinary copper excretion can be challenging due to the overlap with other types of liver disease, particularly during acute hepatic failure or in chronic cholestasis of other etiologies.^[43]

Table 1: Clinical presentations of Wilson disease in children. (Reproduced from,^[1] with permission)

Clinical manifestations	Signs/symptoms	Prevalence	Age at onset (years)
Hepatic	- Increased serum transaminases - Acute hepatitis - Hepatomegaly - Fatty liver - Acute liver failure with hemolysis - Portal hypertension: esophageal varices, splenomegaly, thrombocytopenia - Decompensated cirrhosis with ascites	60%-70% ^[17,20]	>2
Neuropsychiatric	- Dysarthria - Dysphagia, excessive salivation - Mood/behavioral changes including depression, irritability - Incoordination (e.g., handwriting deterioration) - Declining performance at school - Resting and intention tremors - Gait disturbance, dystonia, rigidity - Mask-like face, risus sardonicus, - Stroke-like symptoms	20% ^[30]	>10-15
Ophthalmologic	- Kayser-Fleischer rings: gold or grey-brown opacity in the peripheral cornea (copper deposition on Descemet membrane), seen by slit-lamp examination or with naked eye Sunflower cataract * Always present in neurological involvement ^[33]	<5%	>6-8 ^[7,34]
Hematological	Coombs negative acute intermittent/chronic hemolytic anemia	7% ^[21]	>7 (earliest age of 3 years)
Other:		-	-
Renal	Renal tubular dysfunction Nephrolithiasis Nephrocalcinosis		
Cardiac	Cardiomyopathy, heart failure Arrhythmia		
Musculoskeletal	Rickets/osteopenia/osteoporosis Arthropathy		
Endocrine	Hypoparathyroidism Infertility and miscarriages		
Skin	Lipomas, hyperpigmentation		
Pancreas	Pancreatitis		
Asymptomatic	Detected on family screening Incidental finding of abnormal liver enzymes	-	-

Penicillamine challenge test has been introduced since 1992 for the diagnosis of WD in children.^[44] By giving two doses of 500-mg penicillamine at 0 and 12 h during 24-h urine collection, a cut-off value of 25 $\mu\text{mol}/24$ h provides a sensitivity and specificity of 76% and 93%, respectively.^[45] The test provides a higher sensitivity (up to 92%) in symptomatic patients but could be lower (46%) in asymptomatic patients. By lowering the cut-off to 5 times the upper normal limit of basal 24-h urinary copper level (3.2 $\mu\text{mol}/24$ h), the sensitivity can be increased to 88% but with a lower specificity of 24.1%.^[36] The penicillamine challenge test is not necessarily required if the basal urinary copper excretion is lower than 0.64 $\mu\text{mol}/24$ h.

Urinary copper to creatinine ratio or spot urinary copper, although appears to be correlated with 24-h urinary copper excretion,^[46,47] has not been recommended for the diagnosis of WD. Few studies proposed cut-off values of 0.5 mmol/L and 0.1 mmol/mmol Cr for spot urine copper and the ratio with creatinine, respectively.^[46,47]

c. Liver copper

A liver biopsy is recommended when there is a suspicion of other or additional liver pathology, or the clinical signs and other noninvasive biochemical tests do not provide a definite diagnosis.^[43] The measurement of hepatic parenchymal copper concentration is essential as there is limited diagnostic value on liver histology alone or copper deposition identified by rhodanine, orcein, or rubeanic acid staining.

Liver histology in WD is nonspecific; this includes steatosis, irregular-shaped cytoplasmic inclusions, copper deposition, glycogen-containing vacuoles in the nuclei, lipofuscin and iron deposition (in those with hemolysis), and portal fibrosis and inflammation similar to autoimmune hepatitis.^[1,20] The positive staining can be seen in many cholestatic liver diseases; conversely, negative staining does not help exclude WD.^[48]

Hepatic copper concentration of >250 $\mu\text{g}/\text{g}$ dry weight liver is accepted as a cut-off value for WD, given its sensitivity

Table 2: The scoring system for the diagnosis of Wilson disease (Ferenci score)^[35] (Reproduced from,^[35] with permission)

Score	-1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms suggestive of WD (or typical brain MRI)		Absent		Present	
Coombs-negative hemolytic anemia+high serum copper		Absent	Present		
Urinary copper (in the absence of acute hepatitis)		Normal	1-2×ULN	>2×ULN or normal, but >5×ULN 1 day after challenge with 2 × 0.5 g D-penicillamine	
Liver copper quantitative	Normal		<5×ULN (<250 µg/g)	>5×ULN (>250 µg/g)	
Rhodanine positive hepatocytes (only if quantitative Cu measurement is not available)		Absent	Present		
Serum ceruloplasmin (nephelometric assay)		>0.2 g/L	0.1-0.2 g/L	<0.1 g/L	
Disease-causing mutations detected		None	1		2

Assessment of the WD diagnostic score: 0-1: unlikely; 2-3: probable; 4 or more: highly likely. ULN, upper limit of normal; WD, Wilson disease

of 65.7%–94.4%, with a specificity of 52.2%–98.6%.^[42] Of note, hepatic copper content can be underestimated due to sampling error or increased in other liver diseases with impaired biliary excretion of copper. For an accurate interpretation, two biopsy specimens if possible, with an adequate size of >1 cm (minimum 0.5 cm), are placed on a small piece of paper for drying and in a dry plastic copper-free container.^[1]

d. Serum ceruloplasmin

Ceruloplasmin functions as a copper carrier (95% of total circulating copper) and acts as an antioxidant. Serum ceruloplasmin level can vary with patients' age—low in neonates (<6 months) and peak in mid-childhood.^[49,50] Therefore, serum ceruloplasmin is recommended as a diagnostic tool for children aged >1 year. However, the level of ceruloplasmin can be affected by other liver diseases, malnutrition, and inflammatory conditions, as this protein is largely produced from the liver and functions as acute-phase protein. For example, in WD patients with active infection, serum ceruloplasmin can be elevated to be within normal range, or the level can be low in non-WD patients with protein-losing enteropathy.

Serum ceruloplasmin can be measured by different methods, including enzymatic assays and immunologic or antibody-dependent assays. Enzymatic assays are the preferred method as it detects copper-dependent oxidase activity. While immunologic assays measure both apoceruloplasmin and holoceruloplasmin, which could overestimate serum ceruloplasmin,^[1,51] current WD guidelines^[1,24,43] suggest a cut-off level (<0.2 g/L) indicative of WD that is measured by immunologic methods. Several studies^[36,50,52] proposed different thresholds to better diagnose WD. In patients presenting with liver dysfunction and/or neurological manifestations, a level of <0.14 g/L gave a sensitivity and specificity of 93% and 100%, respectively.^[52] In asymptomatic children with elevated liver enzymes, a level of <0.2 g/L provided sensitivity

and specificity of 95% and 85%, respectively.^[36] Of note, approximately 20% of children and adults with WD may have normal serum ceruloplasmin level.

e. Mutational analysis

Mutational analysis has become a more important diagnostic tool for WD as it can distinguish healthy heterozygote carriers from affected presymptomatic WD patients,^[7] and confirm the diagnosis of WD.^[53] Although mutant alleles can be identified with next-generation sequencing in 95% of affected subjects, the genetics test may be less accessible in some countries and results may take time. Additionally, some patients may require further molecular analysis, including multiplex ligation-dependent probe amplification (MLPA) to search for large gene defects such as whole-exome deletions or duplications, which are not easily identified by direct DNA sequencing.^[7,53]

To date, approximately 900 mutations within the *ATP7B* gene have been identified,^[20,53] and most affected individuals are compound heterozygotes. If only one known mutation is identified, the child is either a heterozygote carrier or a WD patient in whom the second mutation is not yet identified. Several case series^[54-57] reported that 1%–27% of WD patients have only one detected *ATP7B* variant; this could be due to incomplete genetic analysis. Of note, the most complete genetic analysis could provide a detection rate of 77%–98%;^[54,58] this could allow a few cases to have only one or no *ATP7B* variant.^[53] In this case, WD is highly likely if the laboratory tests are suggestive^[7] and the diagnosis can be reached according to WD diagnostic score [Table 2]. A recent study proposed a promising method to directly measure the level of *ATP7B* peptides; this method could provide direct evidence of the consequences of the detected variants even if no second mutation was detected.^[59]

Although it is rare that some children do not have any identifiable mutation, the diagnosis in this group can be

established by long-term follow-up and evaluation of treatment responses. It is worth noting that other hepatic diseases or genetic disorders may mimic a WD-like picture, including congenital disorders of glycosylation, progressive familial intrahepatic cholestasis (MDR3 deficiency), mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratoderma (MEDNIK) syndrome, and idiopathic/primary copper toxicoses.^[53]

Genetic counseling is essential for families of WD patients and screening first-degree relatives is recommended by both European and North American guidelines.

TREATMENT

The aims of treatment are to reduce copper levels (by reducing absorption or removing the excess copper) and prevent its accumulation in the liver and other organs, especially in the central nervous system.

Dietary copper restriction may not prevent copper accumulation; however, excessive consumption of copper-rich food (shellfish, nuts, chocolate, mushrooms, and organ meats such as liver) should be avoided until remission of symptoms and improvement of biochemical abnormalities.^[1]

a. Pharmacological treatment

The goal is either to increase urinary or fecal copper excretion or to block the intestinal absorption of copper. Treatment should commence once the diagnosis is established.^[1]

Although there is limited high-quality evidence to recommend which drug should be used as the optimal first-line treatment in WD, penicillamine is still a standard first-line therapy since it was introduced in 1956. Penicillamine contains a free sulfhydryl group to bind copper and is excreted via the urine. Penicillamine not only increases urinary copper excretion but also induces the endogenous hepatic metallothionein to detoxify copper ions.^[60] The initial dose for children is 150–300 mg/day, with a gradual increase (weekly) up to 20 mg/kg/day divided into two or three doses, or a total of up to 1000 mg (max 1500 mg) in young adults, given in two or four divided doses.^[20] It is essential to start with a low dose and then slowly titrate to the target dose as some patients (particularly in those presenting with neurological signs and symptoms) experienced paradoxical worsening of neurological symptoms during the introduction of penicillamine therapy. This unexpected neurological deterioration tends to be reported mainly in patients treated with penicillamine,^[61]

although it could be found in approximately 10% of cases regardless of drug types.^[17] The adverse effects of penicillamine include hypersensitivity reactions, fever, neutropenia, thrombocytopenia, lymphadenopathy, and proteinuria, which could improve after stopping the medication. Penicillamine could also interfere with pyridoxine metabolism (pyridoxine antagonist); thus, supplementation of pyridoxine should be given orally at the dosage of 25–50 mg/day.^[24]

Trientine was introduced in 1969 as a second-line chelating agent for WD patients, especially in those who experienced side effects from penicillamine. Trientine has increasingly been used as first-line therapy, although the drug could also worsen neurological symptoms. Trientine increases copper excretion via urine by forming a stable complex with the four constituents nitrogen in a planar ring.^[24] Trientine can be started with 20 mg/kg/day in children or 1000 mg (max 1500 mg) in young adults, given in two or three divided doses. As the weight-based dose has not been established yet, the dose can increase up to 900–1500 mg/day in two or three divided doses during maintenance.^[20] Trientine also chelates iron and thus could lead to iron deficiency anemia or sideroblastic anemia. However, iron supplement should be given at a different time from trientine because trientine-iron complex is nephrotoxic.

Zinc acts differently from penicillamine and trientine; instead of increasing urinary copper excretion, it interferes with copper uptake from the gastrointestinal tract. Zinc increases fecal copper excretion by inducing enterocyte metallothionein to complex with copper and inhibiting the entry of this complex into the portal circulation.^[62] Additionally, zinc could increase the level of hepatic metallothionein and thus could prevent hepatocellular injury from copper toxicity.^[63] Zinc therapy has been used as first-line monotherapy in patients with neurological WD. However, it should be used with caution in hepatic WD patients and is not recommended in symptomatic patients. Gastric irritation or actual gastritis is the most common adverse effect of zinc therapy, dependent on the type of zinc salt used.^[17,20,24,43]

Ammonium tetrathiomolybdate could chelate copper very effectively; however, clinical trials are being initiated in children in Europe and North America. It acts by binding copper in the intestinal tract, thus preventing copper absorption and making copper unavailable for cellular uptake.^[43,64] In a randomized control trial, tetrathiomolybdate appeared to work more efficiently as compared to trientine in terms of neurologic preservation in adult WD patients with neurological involvement.^[65]

The dosage, administration, and adverse effects of the drugs are summarized in Table 3.

b. Liver transplantation

Indications for liver transplantation (LT)^[67] in patients with WD are those with ALF, as defined by the rapid development of severe hepatic insufficiency with coagulopathy and with hepatic encephalopathy, with progression of liver dysfunction to liver failure despite drug therapy, and those with acute or chronic liver failure due to WD.^[1,17,43] LT in patients with neurologic WD is still controversial.

Children presenting with ALF without hepatic encephalopathy can be treated with chelation agents; however, the response to medication may take time given it can take at least 1 month for the improvement of prothrombin time and 3–12 months for normalization.^[68] It could be challenging to decide when WD patients require LT; the revised King’s prognostic WD Index has been proposed to evaluate those who most likely fail on chelation or die without LT [Table 4]. The index score of ≥ 11 was a strong predictor of mortality without LT, with a sensitivity and specificity of 93% and 97%, respectively. The score also provided high positive and negative predictive values of 92% and 97%, respectively.^[69] A recent study prospectively re-evaluated the WD index and proposed that patients with an index of 8–10 within the first 2 weeks of admission

require close monitoring for at least 2 months, as the disease could progress and LT may become necessary (*Chanpong and Dhawan. Re-evaluation of King’s Wilson Index in children with acutely decompensated hepatic Wilson disease, manuscript under review*).

c. Future therapeutic strategies: liver cell transplantation and gene therapy

Human hepatocyte transplantation has shown promising results in various animal models, although there are some concerns regarding the shortage of donor organs, low cell engraftment, and a lack of long-lasting effects.^[70,71]

Another alternative therapy option is the genetic correction of the *ATP7B* gene or gene therapy. Currently, its practical application still requires further investigation, although good outcomes have been reported in experimental animal models by using an infusion of recombinant adeno-associated virus bearing *ATP7B* cDNA.^[72-75] A recent study reported the use of CRISPR/Cas9 technology to correct *ATP7B* point mutation frequently detected in WD patients.^[67] However, clinical studies for WD gene modification are required so that these could become alternative curative strategies in the future.

FOLLOW-UP AND PROGNOSIS

In patients without advanced liver or brain injury, liver function can improve in >90% of patients, usually

Table 3: Drug administration and monitoring.^[1] (Reproduced from Ref, 1 with permission)

	Penicillamine	Trientine	Zinc acetate/sulphate	Ammonium tetrathiomolybdate
Initial dosage	150-300 mg/day, gradually increasing once a week up to 20 mg/kg/day given in 2 or 3 divided doses or 1000 mg (max 1500 mg) in young adults given in 2 or 4 divided doses	20 mg/kg/day or 1000 mg (max 1500 mg) in young adults given in 2 or 3 divided doses	Age >16 years and body weight >50 kg: 150 mg/day in 3 divided doses. Age 6-16 years and body weight <50 kg: 75 mg/day in 3 divided doses Younger than 6 years: 50 mg/day in 2 divided doses	20 mg 3 times daily with meals and 20 mg 3 times daily between meals (doses in adult trials) ^[65]
Maintenance dosage	10-20 mg/kg/day up to 750 mg-1000 mg/day in 2 divided doses	900-1500 mg/day in 2 or 3 divided doses	same	200-260 mg/day (in adults) ^[66]
Administration	1 h before meal or 2 h after meal	1 h before meal or 3 h after meal	1 h before meal or 2 h after meal	
Supplements	Pyridoxine	Iron	nil	nil
Parameters for adequate treatment	Urinary copper excretion: 3-8 $\mu\text{mol/L/24 h}$ on maintenance treatment	Urinary copper excretion: 3-8 $\mu\text{mol/L/24 h}$ on maintenance treatment	Urinary copper excretion 0.5-1.2 $\mu\text{mol/L/24 h}$ on maintenance treatment Serum zinc >125 mg/dL Urinary zinc >2 mg/24 h on maintenance treatment	N/A
Time to improvement	2-6 months	2-6 months	2-6 months	not known
Adverse effects	Hypersensitivity reactions, fever, neutropenia, thrombocytopenia, lymphadenopathy or proteinuria	allergic reactions, arthralgia, sideroblastic anemia	Gastric irritation (e.g., nausea, abdominal pain, gastric ulcerations), immunosuppressive effects, reduced leukocyte chemotaxis, hyperlipasemia, and/or hyperamylasemia	Bone marrow depression, hepatotoxicity, overly aggressive copper removal causes neurological dysfunction

Table 4: The revised King's prognostic Wilson Index^[69] (Reproduced with permission)

Score	Bilirubin (μmol/L)	INR	AST (IU/L)	WCC (×10 ⁹ /L)	Albumin (g/L)
0	0-100	0-1.29	0-100	0-6.7	>45
1	101-150	1.3-1.6	101-150	6.8-8.3	34-44
2	151-200	1.7-1.9	151-300	8.4-10.3	25-33
3	201-300	2.0-2.4	301-400	10.4-15.3	21-24
4	>301	>2.5	>401	>15.4	<20

over 2–6 months. Neurological improvement is observed in 50%–60% of patients over a longer time course of 1–3 years if early and correct pharmacological treatment has been introduced.^[43]

Most importantly, adherence to the therapy is essential for long-term success. A recent study has proposed the use of 24-h urinary copper excretion to monitor adherence in children with WD.^[76] This study suggested that the level of 24-h urinary copper should drop to ≤8 μmol/day and <6 μmol/day after 1 and 5 years of treatment, respectively.

PREVENTION AND SCREENING

Prevention of an inherited disease could be challenging; therefore, early detection and treatment are the main goals in this context. Genetic counseling is necessary, and systematic family-wide screening (not only in first-degree relatives) is recommended for the families of WD patients.^[24,43,53] The assessment should include history taking, physical examination, biochemical tests (liver function tests, serum ceruloplasmin, and urinary copper excretion), and molecular testing for *ATP7B* mutations. This should be considered particularly in both parents of the affected child, as well as all available siblings.^[1] If the sibling carries homozygous *ATP7B* gene variants or the same compound heterozygous of the index patient, other diagnostic tests could be omitted.^[53]

SPECIFIC ISSUES IN YOUNG ADULTS COMPARED TO CHILDREN

As mentioned earlier, neurological or psychiatric disease is more prevalent in older children and young adults (aged 20–30 years old)^[1,17] and could be misdiagnosed as psychosis.^[77,78] Generally, NAFLD appears to be more common in early adolescence (age: 12–15 years)^[25] and hence may delay the diagnosis of WD. Because disease prognosis depends on the prompt initiation of therapy, WD should be considered in young adults presenting with neurologic or psychiatric symptoms and/or NAFLD.

One of the most challenging issues in teenagers is their compliance to medical treatment, especially in those with

chronic disease like WD. Non-adherence could negatively affect the treatment outcome.^[79] Apart from that, alcohol consumption, smoking and illicit drug use could also worsen liver disease. Thus, WD patients should be advised to avoid alcohol consumption and other potential hepatotoxic drugs.^[1]

Another important issue is the surveillance of hepatocellular carcinoma (HCC). Approximately 4% of patients could develop abdominal malignancy, including HCC, after 10–19 years of follow-up.^[80] This incidence becomes higher as the duration of follow-up increases. Therefore, screening and surveillance for HCC is recommended for WD patients, especially in those with cirrhosis.

a. Fertility and pregnancy

Counseling in young adults regarding fertility and therapeutic management during pregnancy and lactation is also essential. Untreated or poorly controlled female WD patients can have menstrual and ovulatory dysfunction due to liver dysfunction and copper intoxication of specific enzymes that are involved in the normal menstrual cycle and ovulatory mechanism. This could reduce their fertility or lead to early pregnancy complications (e.g., spontaneous abortion). By commencing chelating therapy to achieve adequate copper control and recover liver function, the ovulatory disturbances can be reversed. This also emphasizes the necessity of pre-pregnancy copper chelation therapy.^[81,82]

Pregnant women with WD should continue on the same medication that they have been on already to avoid exacerbation of symptoms.^[82,83] Ideally, a hepatologist with experience in WD should supervise on the treatment during pregnancy. The dosage of penicillamine and trientine can be decreased to the minimum necessary to maintain clinical and biochemical stability,^[43] especially during the first trimester, as the risk of fetal teratogenicity is high in the first trimester, and the last trimester to avoid insufficient copper supply to the fetus and/or insufficient wound healing after caesarean section or episiotomy.^[24] After delivery, the same level of chelating agents as used before pregnancy is recommended. Regular clinical evaluation and assessments of liver function tests and copper monitoring in blood and urine are essential both during and after pregnancy.^[82] As all chelating agents are excreted into the breast milk, breast feeding is not recommended during lactation.^[43]

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Conflicts of interest

AD- consults for Univar, Alexion, Orphalan, Novartis, MSD and Johnson and Johnson.

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