Wilson disease in children and adolescents

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Received 3 November 2019
Revised 18 December 2019
Accepted 19 December 2019

To cite: Fernando M, van Mourik I, Wassmer E, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2018-315705

ABSTRACT

Wilson disease (WD) is a rare, recessively inherited disorder of copper metabolism mainly affecting liver and brain. In childhood, it is known to have a predominant hepatic phenotype. It is likely that the low awareness for WD-associated neuropsychiatric signs and symptoms in this age group means that neurological Wilson's disease is underdiagnosed in children and young people. Practitioners should be alert for this complication in children with or without liver disease. Management of children with WD requires a dedicated multidisciplinary approach involving hepatologists, geneticists, neurologists and psychiatrists to ensure subtle neuropsychiatric symptoms are identified early and addressed appropriately. This review highlights recent advances in hepatic and neuropsychiatric symptoms of WD in childhood, specific diagnostic tools and pitfalls and summarises existing and potential future treatment options.

What is already known?

- Wilson Disease is rare and with predominant hepatic phenotype when presenting in childhood.
- Screening for Wilson disease (WD) should be part of the investigation panel of any child with liver abnormalities.

What this study adds?

- Raised awareness of neuropsychiatric manifestations of WD in childhood:
  - regular detailed neurology and psychiatric history and neurology exam should be part of routine care. MRI brain can be done at baseline and as symptoms occur.
  - Neurological WD can present without evidence of hepatic disease
- Due to the complex clinical presentation and course, children should be seen by a multidisciplinary team assessing the various aspects of WD.
- More discriminative, rapid diagnostic tests for WD (exchangeable copper and relative exchangeable copper) are being explored for regular use in clinical practice. Positive results would allow treatment start without waiting for genetic test results.
- New drugs (trientine tetrahydrochloride (Cuprior), bis-choline tetrathiomolybdate (Decuprate)) have been developed and are under review for use in the UK.
- Exciting research progress is made into development of curative strategies for WD(eg, gene therapy, cell therapy and correction of dysfunctional *ATP7B* mutant function).

BACKGROUND

Wilson disease (WD) is a rare, recessively inherited disorder of copper metabolism due to mutations of the ATP7B gene. The resulting copper toxicosis mainly affects liver and brain. Early treatment improves long-term outcome.

WD in childhood has been considered to have a predominant hepatic phenotype. Neuropsychiatric involvement is well described in adults with WD but general awareness of its signs and symptoms in childhood, particularly in the absence of hepatological signs and symptoms, is low and probably underestimated.

There are no data on the clinical prevalence of WD, but the global genetic prevalence is estimated around 1:7026. Heterozygosity in UK was predicted to be 2.5% of the general population. Published data by the Euro Wilson database reported 415 new cases from 2005 to 2009 with approximately half of the cases being less than 18 years of age.[1 2]

The significant inconsistency between the number of clinically encountered WD and estimated genetic prevalence may be due to genetic phenotypic heterogenicity and/or low rates of diagnosis, particularly in the paediatric age group when children present with subtle neuropsychiatric signs and symptoms, but WD is not considered in the differential diagnosis.

This review will review new developments in diagnosis and management of WD and focus on the neuropsychiatric signs and symptoms in children with WD.

GENETICS AND EPIGENETICS

More than 700 disease-causing mutations of ATP7B gene have now been identified. The majority of patients are either homozygous or compound heterozygous for common mutations, with H1069Q being the most common mutation in Europe and North America, and Arg778L in Asia. However, unusual genetic scenarios, including presence of three different missense mutations and cases of segmental uniparental isodisomy, have been reported. Negative mutational analysis does not exclude WD.

More genotype–phenotype correlation studies are needed to understand discordance between phenotype and different liver and neuropsychiatric outcomes.[3 4]

PATHOPHYSIOLOGY

In WD, copper transporting P-type ATPase is defective due to mutations of ATP7B gene, which is

predominantly expressed in hepatocytes, but also in the brain, breast and placenta. Defective ATPase leads to reduced synthesis of ceruloplasmin and reduced export of copper from cells, resulting in progressive copper accumulation in affected organs.[5]

Excess copper adversely affects mitochondrial function of hepatocytes causing impaired energy utilisation and downregulation of cholesterol synthesis leading to steatosis. Chronic injury leads to inflammation or hepatitis and attempted repair results in fibrosis.

With time, non-ceruloplasmin bound copper accumulates in other organs including brain, cornea and kidneys, leading to copper-induced free radical-mediated cellular damage. Long-term exposure to high copper causes astrocyte damage and demyelination in brain, mostly in the basal ganglia and thalamus. High free copper in the blood causes non-immune haemolysis by oxidative damage. Renal tubulopathy occurs due to raised copper in renal medulla.

CLINICAL MANIFESTATIONS

The average age at presentation in childhood is 13.2 years (range 5–35 years). Presentation before 3 years of age is unusual as it takes time for the copper toxicosis to build up within the body. The clinical phenotype of WD is diverse (table 1). Most children present with overt hepatic disease, though subtle neurological disease may already be present. Older children, young people and adults WD may present with neurological or psychiatric disease, and this diagnosis, even in the absence of liver disease, should not be overlooked.

Hepatic manifestations

Liver disease is the first presentation in up to 60% of patients with WD in all age groups. It may be completely asymptomatic and be a coincidental finding or present with signs and symptoms of any form of liver disease. Progression may be slow or very rapid. Screening for WD should be part of the investigation panel of any child with liver abnormalities.

Diagnosis

WD remains difficult to diagnose and dependent on a combination of clinical features, laboratory markers of copper accumulation, histology, dry liver copper concentration and genetic analysis.[6 7]

Findings on clinical examination are generally non-specific and vary from normal to obvious jaundice and chronic liver disease, for example, hepatosplenomegaly, ascites, palmar erythema and spider naevi. Kayser-Fleischer (KF) rings, gold or grey-brown opacity in the peripheral cornea, seen by slit-lamp examination or with naked eye, become more apparent with progression of disease. Presence in suspected WD makes diagnosis highly likely (figure 1).

Biochemical tests should include aspartate transaminase, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), serum bilirubin with conjugated fraction, serum albumin, prothrombin time and glucose to assess liver injury and hepatic synthetic function. A high bilirubin (>300 μmol/L) with relatively low transaminases (100–500 IU/L), GGT and ALP levels are suggestive though not pathognomonic of WD. Coombs negative haemolytic anaemia may be the first presentation. Thrombocytopenia is associated with hypersplenism in established portal hypertension.

Although insufficient on an individual basis, the association of the three key biochemical markers (low serum caeruloplasmin, low serum copper and high urinary copper excretion) is highly predictable of WD diagnosis.

Table 1 Clinical manifstations and multisystem involvement of WD

Clinical manifestations	Red flag signs/symptoms
Hepatic dysfunction (unlikely before 3 years)	Acute liver failure: jaundice, hepatitis, coagulopathy±encephalopathy in a previously well child. Acute hepatitis: intermittent episodes of hepatitis, malaise±jaundice and/or mild coagulopathy. Chronic liver disease: hepatomegaly/splenomegaly/abnormal liver function tests (LFTs), portal hypertension, cytopenia due to hypersplenism, decompensated liver disease or variceal bleeding.
Neurological	Movement disorder ► Parkinson – Rigidity. – Hypokinesia. – Resting tremor. ► Ataxia – Postural and intentional tremor. – Ataxia of limbs. – Dysarthria. ► Dystonia – Dystonic posturing. – Choreathehosis. – Dysphagia. – Hypersalivation. ► Specific – Risus sardonicus – pseudosmile. – Wing-beating – postural tremor of arms. – Stretched arm behind the back. ► Other – Stereotypes. Cognition ► Executive cognition. ► Attention. ► Visuospatial perception and reasoning. ► Learning and memory. ► Verbal and abstract reasoning. ► Processing. Others: ► Neuropathy. ► Autonomic dysfunction – syncope. ► Headaches. ► Seizures. ► Hemiparesis.
Psychiatric (in adolescents and adults)	► Mood disorders (bipolar, depression and anxiety). ► Behaviour and personality (disinhibition, impulsive and aggressive behaviour). ► Psychosis and schizophrenia.
Musculoskeletal/bone and joints	Rickets/osteomalacia and arthropathy/arthritis.
Haematological	Coombs negative acute haemolytic anaemia commonly, intermittent or chronic haemolytic anaemia in some cases.
Renal	Renal tubular dysfunction (Fanconi syndrome, renal tubular acidosis and aminoaciduria), urolithiasis, nephrocalcinosis, haematuria and hyperoxaluria.
Eyes	KF rings: Gold or grey-brown opacity in the peripheral cornea, seen by slit-lamp examination or with naked eye, become more apparent with progression of disease; presence in suspected WD makes diagnosis highly likely. Other eye manifestations Sunflower cataracts and saccadic eye movements.
Other: ► Cardiac ► Skin ► Parathyroid ► Fertility ► Pancreas	Arrhythmias, cardiomyopathy, heart failure pigmentation and a bluish discoloration at the base of the fingernails (azure lunulae). Hypoparathyroidism. Infertility and miscarriages. Pancreatitis.
Asymptomatic	WD detected due to family screening. Incidental finding of raised transaminases.

WD, Wilson disease.

There are a number of pitfalls using these parameters (table 2).[8 9]

► Caeruloplasmin levels may be normal or raised due to hepatic or other inflammatory conditions, and low due to malnutrition and in 15% of carriers for WD mutations.

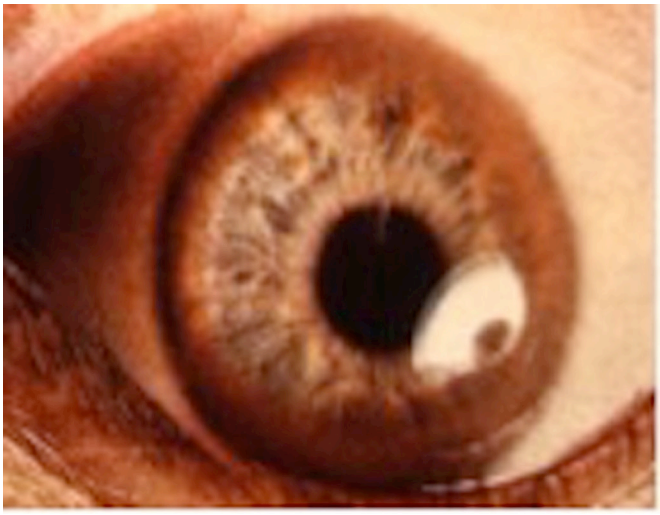

Figure 1 Kayser-Fleischer ring on slit-lamp examination.

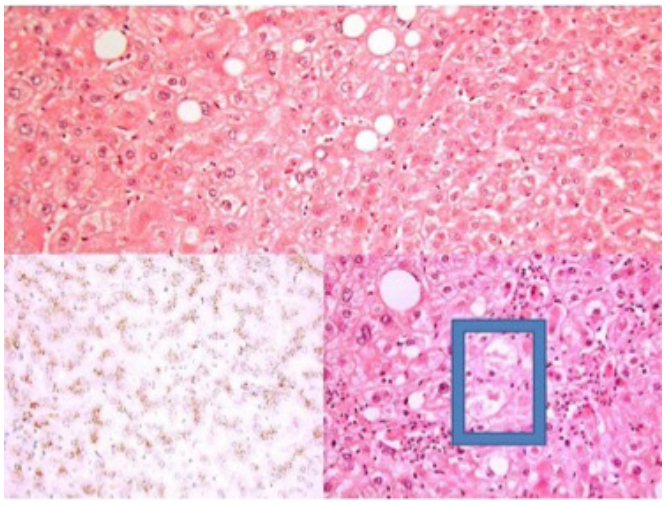

Figure 2 Histological features in Wilson disease. (A) Mild steatosis (H&E ×100). (B) Red/brown copper granules on a rhodanine stain (×200), distinctly patchy change within the liver; absence of copper does not exclude WD. (C) Ballooned hepatocytes (see rectangle), containing Mallory Denk bodies. Note: none of these features is diagnostic in isolation; the clinical setting is required.

- The prepenicillamine urine copper analysis may be normal or inconclusive, in which case a postpenicillamine urine copper analysis should be carried out. This test is unreliable in presymptomatic patients with WD and may be abnormal in heterozygotes.

Alternative, more discriminative tests for WD have been developed and are being explored for regular use in clinical practice. They are rapid, reliable and non-invasive and would allow treatment to start without waiting for genetic test results.[10]

- Exchangeable copper (CuEXC) determination allows direct and accurate measurement of copper overload. It provides, at diagnosis, information on the spread and severity of the disease.
- Relative exchangeable copper (REC) calculation (percentage of exchangeable to total serum copper) is a very valuable discriminative tool for WD diagnosis presenting excellent sensitivity and specificity.

WD diagnosis can be confirmed on liver biopsy tissue. Histological features are non-specific and include fatty deposition, Mallory-Denk bodies (irregular shaped cytoplasmic inclusions), copper deposition, glycogen-containing vacuoles in the nuclei, lipofuscin and iron deposition (in those with haemolysis) (figure 2). Negative copper staining does not exclude WD, whereas positive staining is seen in many cholestatic liver diseases.[11]

Table 2 Biochemical and histological tests for Wilson disease

Test	Value in WD	Pitfalls/comments
Plasma caeruloplasmin	<200 mg/L (in 85%–90% of cases).	Elevated by hepatic or other inflammation. Low in other conditions, for example, malnutrition, aceruloplasminaemia and protein losing enteropathy, infants <1 year. WD heterozygotes may have plasma ceruloplasmin <200 mg/L.
Serum copper	Low, normal or high.	Poor diagnostic value in WD.
Free serum copper (or non-ceruloplasmin bound copper)	>7 (µM).	Estimated from serum copper and serum ceruloplasmin levels but is dependent on adequacy of the methods used measuring both and as such unreliable in diagnosing WD.
Urine copper (prepenicillamine)	>1.25 µmol/24 hours. >40 µg/24 hours in asymptomatic WD. >100 µg/L in symptomatic WD.	May be increased in acute hepatitis but usually much higher in WD.
Urine copper (postpenicillamine)*	>25 µmol/24 hours. >1600 µg/24 hours.	Indicated in symptomatic children if prepenicillamine test is normal or doubtful poor sensitivity in presymptomatic siblings.
Liver histology	Macro or micro vesicularsteatosis, portal or lobular inflammation, fibrosis, Mallory denk bodies, copper staining, canalicular cholestasis glycogenated hepatocyte nuclei.	Negative copper staining in liver biopsy does not exclude WD.
Liver copper	>250 µg/g dry weight (normal <55).	Higher values can be found in newborns and prolonged cholestasis due to other liver diseases (eg, sclerosing cholangitis). In patients with WD with cirrhosis, this value can be <250 µg/g, which can be confusing.
MRI (T1 and T2 weighted)	Detect atrophic changes and changes of the putamen. Giant panda's sign.	
Ophthalmic examination	Looking for KF rings and other eye abnormalities.	

*Penicillamine challenge is undertaken by giving two doses of penicillamine 500 mg at each time, at the beginning and 12 hours following commencement of urine collection.
KF, Kayser-Fleischer.

Table 3 Diagnostic score in WD agreed at consensus meeting

Score	−1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms suggestive of WD (or typical brain MRI)		Absent		Present	
Coombs negative haemolytic anaemia+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.

Liver copper >250 µg/g dry weight is diagnostic and confirms a diagnosis in the context of other results. Higher values are found in newborns and in cholestatic liver diseases, for example, sclerosing cholangitis, and may cause confusion. In patients with cirrhosis, the result may be lower, which may explain why presymptomatic children have higher liver copper content than older symptomatic children.[12]

Molecular testing for ATP7B mutations is essential and in most cases confirms a diagnosis of WD. Direct DNA sequencing can optimise mutation detection (up to 95%) but may identify variants of unknown significance, which pose diagnostic difficulties. Identification of one disease-causing mutation confirms the diagnosis of WD only in the presence of definite clinical symptoms and biochemical signs of impaired copper metabolism. In asymptomatic children, the identification of two disease-causing mutations is necessary to confirm a diagnosis of WD with certainty.[13]

As none of the available laboratory tests is specific for WD, a diagnostic score, based on several clinical signs and laboratory features, was developed (table 3). A score of ≥4, makes the diagnosis highly likely.

NEUROPSYCHIATRIC MANIFESTATIONS

Neurological involvement is well described in adults with WD and includes movement disorders (dystonia, Parkinson, ataxia, dysarthria and tremor), psychiatric disorders and cognitive impairment.[14]

In the paediatric setting, awareness of neurological signs and symptoms of WD is low as it is generally thought these symptoms do not occur until adulthood. However, case series suggest that >5% of children with hepatic presentation of WD already have neurological involvement and that >15% of patients with WD develop neurology symptoms or signs during childhood.[15–17] Many patients with known hepatic WD have educational difficulties suggesting possible WD neurocognitive pathology.[18]

As most treatment is based on halting (and reversing) progression of hepatic WD, it is less well known that neuropsychiatric symptoms may develop or progress despite excellent biochemical response to treatment. In addition, neurological WD may present without obvious hepatological signs and symptoms and so the overall number of paediatric patients with WD may be higher than appreciated.

Diagnosis

Diagnosis is based on clinical presentation and brain imaging.

In contrast to adults with neurological WD, movement disorder signs and symptoms in children are milder, more subtle and therefore more difficult to pick up. In addition, patients/parents may not volunteer these symptoms as the focus is on the liver disease. Main motor symptoms described in children are tremor, mild ataxia and dysarthria with drooling. Very rarely a rapid progressive dystonia occurs.

Psychiatric problems may not be recognised as a symptom of WD. They are common in adults with a quarter having symptoms at presentation and almost all developing symptoms over the course of the disease.[19–21]

Mood disorders with depression and anxiety are seen in up to half of adults with WD and appear to be the main psychiatric symptom in paediatric patients. However, little is known about exact prevalence in this age group. They may be interpreted as an adjustment disorder as children, and especially young adults, are coming to terms with living with a chronic disorder requiring treatment.

Cognitive impairment can be mild initially and occasionally reversible, but in many will deteriorate over time. In children, this will mainly affect attention, learning and processing, but as the child grows up, it will start to affect higher functions including executive cognition (flexibility, planning and decision making), visual spatial skills and verbal reasoning.[18] Cognitive difficulties at school may be ignored and attributed to school absence due to hospital visits, medication side effects and so on.

Many, though not all, patients with WD may have brain abnormalities on MRI. Changes can be present before detection of neurological or liver manifestations and some may reverse following copper chelating treatment. There are limited numbers of studies reporting MRI findings of the brain in children with WD.[22–24]

High-signal intensity lesions in the basal ganglia on T1-weighted images generally reflect hepatic involvement of WD, that is, changes secondary to chronic liver disease. High signal intensity lesions on T2-weighted images reflect cerebral involvement of WD. The latter typically include changes in the deep grey matter (putamen, caudate and thalamic nuclei) and the mescencephalic and pontine white matter, as well as atrophy (not reported in children with WD) (figure 3).[25–28]

Magnetic resonance spectroscopy can detect heavy copper accumulation in brain matter and be a non-invasive study of brain metabolism. It detects metabolite abnormalities before structural changes become visible on MRI, and its use has been well described in adults with WD. Recent studies in paediatric WD confirmed this imaging modality detects early neurological changes even with normal MRI and could provide crucial information for monitoring disease progression.[29]

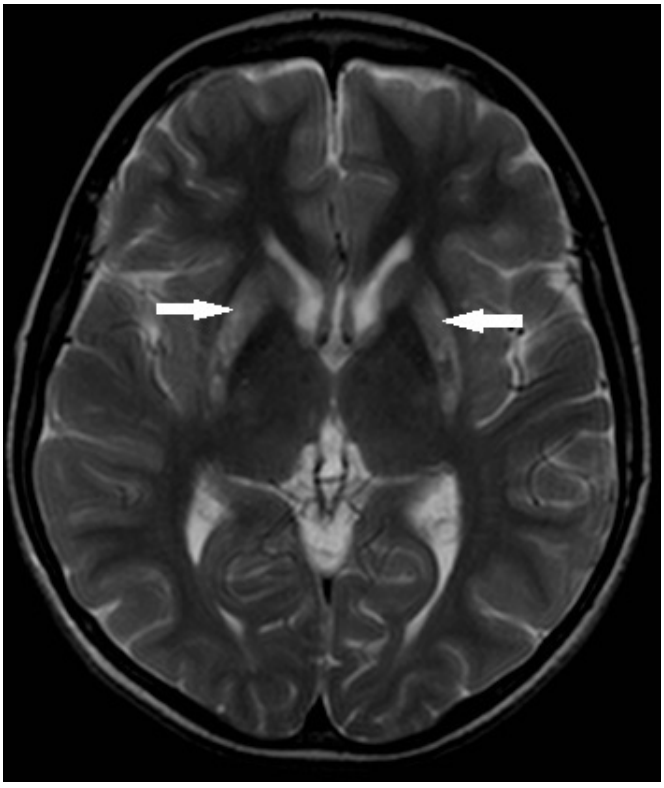

Figure 3 T2-weighted MRI brain image: arrow shows bilateral abnormal high signal in putamen and dark globus pallidus.

Treatment options

Conventional drug therapy for WD focuses on the removal of copper excess (decoppering) either through promoting copper excretion by chelating agents such as D-penicillamine and trientine, by blocking intestinal copper absorption with zinc salts, or both. Although not recommended as sole therapy, high copper-containing foods (eg, chocolate, dried fruit, liver, sesame seeds and sesame oil, and shellfish mushrooms and nuts) should be avoided until normal liver biochemistry is achieved with chelators (table 4).[6 7]

With successful medical therapy, improvement in LFTs are expected within 3–6 months and normalisation of ALT within 1 year. In most patients, following normalisation of LFTs, the liver will remain compensated for the rest of their lifespan. Type of medication and/or dose should be changed if not tolerated, significant adverse effects or persistently raised INR >1.5 or ALT >3 times.

Penicillamine is used as first-line treatment in acute and/or symptomatic WD. It binds to copper and is excreted via the urine. Though highly effective, it is associated with serious adverse side effects, requiring discontinuation of the drug in up to 30% of patients. Paradoxical worsening of neurological symptoms of WD following introduction of penicillamine therapy is well described and improves or stabilises after withdrawal of the drug. Those with chronic liver disease, leucopenia and/or thrombocytopenia appear to be most at risk.[30]

Trientine dihydrochloride was introduced as second-line drug for patients intolerant of penicillamine. It promotes copper excretion via the kidneys, is equally effective and has similar though less frequently occurring side effects to penicillamine. It is a logic first-line treatment but, due to its high costs, is approved for use in the UK as second-line chelator in patients intolerant to penicillamine only.[31]

Trientine tetrahydrochloride (Cuprior) is a hybrid medicine containing a different form of trientine with similar benefits and risks to trientine dihydrochloride. The main advantage is improved trientine release in the body so that a lower dose achieves a good patient response, which makes it more cost effective. It has been approved in the European Union for the treatment of WD in adults, adolescents and children aged 5 years and older who are intolerant to penicillamine and is currently under review for use in the UK.[32]

Zinc salts are used in combination with penicillamine for the initial management of symptomatic patients. They are effective and safe as first choice treatment in presymptomatic patients and as maintenance therapy for stable patients whose disease has been stable on penicillamine or trientine. Safety and efficacy have been demonstrated in neurological WD, and they could be considered first-line therapy in this setting. The working mechanism is through activation of metallothionein in intestinal cells,

Table 4 Pharmacological treatment of Wilson disease (WD)

Drug	Dose	Reported side effects
D-Penicillamine*	Starting dose: 150–300 mg/day, gradually increasing once a week up to 20 mg/kg/day in two or three divided doses, or 1000 mg (max 1500 mg) in young adults, given in 2–4 divided doses. Maintenance dose: 10–20 mg/kg/day up to 750–1000 mg/day in two divided doses.	Skin: urticaria, cutis laxa, elastosis perforans serpiginosa, lichen planus and aphthous stomatitis. Renal: proteinuria/nephrotic syndrome. Marrow suppression: neutropenia/thrombocytopenia Others: drug-induced lupus, lymphadenopathy, worsening of neurological features of WD and pyridoxine deficiency.
Trientine (trientine dihydrochloride)	Starting dose: 20 mg/kg/day or 1000 mg (max 1500 mg) in young adults given in 2–3 divided doses, adjusted to clinical response. Maintenance dose: 900–1500 mg/day in two or three divided doses, adjusted to clinical response.	Drug-induced lupus, colitis, arthralgia, muscle cramps and sideroblastic anaemia when given with zinc worsening of neurological features.
Trientine Tetrahydrochloride	Children >5 years only: 225–600 mg/day (1 ½ to 4 tablets daily), in 2–4 divided doses.	Nausea, gastro-intestinal upset and inflammation, itching, skin rash, urticarial and iron-deficiency anaemia have been reported.
Zinc salts (zinc acetate and zinc sulfate)	<6 years: 25 mg twice a day. 6–16 years or if <50 kg: 25 mg three times a day. >16 years or if >50 kg: 50 mg three times a day.	Dyspeptic symptoms, nausea, abdominal pain, gastric irritation, gastric ulceration, iron deficiency, raised amylase and lipase.
Bis-choline Tetrathiomolybdate	30 mg twice a day.	Significant side effect profile of bone marrow depression and epiphysial abnormalities and hence clinical use is limited.

*Should also have pyridoxine 50 mg/week; administered on empty stomach; cytopenia, hypersensitivity and proteinuria warrant immediate discontinuation of therapy and switching to other modes.

thus promoting copper binding in the enterocyte and reducing absorption of copper from the gut.[33 34]

Bis-choline tetrathiomolybdate (TTM; Decuprate) is a new drug for treatment of WD presenting with acute neurological disease as conventional chelator therapy could lead to rapid and irreversible clinical deterioration. It has been used extensively in veterinary practice for the treatment of acute copper poisoning in sheep. TTM does not directly bind to copper and therefore is not a chelator. It increases biliary copper excretion through formation of a stable three-way complex with copper and albumin. Unlike conventional chelators, it can cross the blood–brain barrier for consequent uptake in neuronal cells. The full mode of action is still not fully understood but TTM appears to inhibit hepatocellular and neuronal uptake of copper and induces negative copper balance by promotion of biliary secretion. Liver injury may occur but is dose dependent. Phase III clinical trials are underway to assess efficacy and safety in patients (>18 years) with WD.[35–37]

Treatment may improve hepatic damage and/or prevent development or further deterioration of neurological and psychiatric manifestations of WD. Treatment of either liver or brain disease needs to be lifelong without any interruption. Discontinuation of maintenance treatment will lead to recurrence of symptoms, liver failure and neurological deterioration. Monitoring of treatment is important to ensure efficacy, safety and compliance. Sadly, the disease may progress despite treatment, particularly in those with neuropsychiatric disease.

Monitoring

In patients on penicillamine and/or trientine, a 24-hour urinary copper excretion should be monitored periodically. Urinary copper excretion should increase when treatment is started, followed by a decrease once biochemistry is normal, and stabilise between 200 µg and 500 µg/24 hours indicating a reduction of body load of copper. Presymptomatic children excrete less copper.[6 7]

Patients on zinc monotherapy should have regular monitoring of serum and urinary zinc levels, which should be maintained above 125 µg/dL and 1.5–2 g/day respectively. Urinary copper levels below 30 µg/24 hours suggest zinc overdose.

Liver transplantation (LTx)

LTx is indicated for those patients with liver disease who do not respond to medical treatment, who have fulminant or advanced liver failure and/or significant portal hypertension. LTx is curative, restoring biliary copper excretion, KF rings disappearing over time, but neurological damage may persist.[38 39]

Whether LTx is indicated for progressive neurological WD without liver failure is debatable. Reports suggest improvement or at least stabilisation of neurological manifestations in those receiving an LTx for liver disease. Although still highly controversial in patients with severe neuropsychiatric symptoms, there is growing evidence that patients with predominant neurological symptoms but otherwise stable liver function may stabilise or even improve after LTx and should therefore be considered for pre-emptive LTx.[40 41]

Living-related LTx using a heterozygote for WD donor is successful thus expanding the donor pool. Up to a third of WD heterozygotes have abnormal serum copper and caeruloplasmin levels but will not develop liver disease, and recipients of those grafts have excellent survival and improvement in copper metabolism without recurrence of WD.[41]

Family screening

Genetic counselling is essential for families with WD, and screening of first-degree relatives is recommended as the chance of being a homozygote and developing clinical disease is 25%. Screening should include physical examination, serum caeruloplasmin, liver function tests and molecular testing for ATP7B mutations or haplotype studies.[6 7]

Treatment with zinc should be started as soon as a diagnosis is confirmed and in young children from 3 years of age or sooner if liver function is abnormal.

FUTURE DIRECTIONS

Although current medical and surgical therapies are effective in the treatment of most patients with WD, novel strategies to cure WD through correction of the cellular defect are being developed, as well as developing tools, for example, biomarkers, to diagnose WD early and monitor therapeutic impact.

Emerging curative strategies include:

Gene therapy aims to correct the defect in native hepatocytes by providing healthy copies of *ATP7B* via introduction of transgene vectors that integrate and/or persist in cells.[42]

Cell therapy through human hepatocyte transplantation is used to treat many liver metabolic disorders. In WD, it could repopulate the liver with functionally intact cells that can reverse biliary copper excretion and potentially cure WD. There are practical issues to be resolved, including the need for multiple donors of hepatocytes, repeat infusions if adequate cell survival or repopulation is not achieved and lifelong immunosuppression.[43]

Correction of dysfunctional *ATP7B* mutant function and/or less toxic suppression of copper import is being explored, following the model of modulators already widely explored in cystic fibrosis.[44]

CONCLUSION

WD is rare and predominantly presents with liver disease in childhood. Neuropsychiatric symptoms, common in adults with WD, are less well appreciated in childhood, due to a combination of lack of awareness, experience and their subtle nature at presentation. It is now understood that neurological disease in children and young people may present in the absence of obvious liver disease. Families should be counselled about the development and potential progression of neuropsychiatric symptoms despite good biochemical response to medical treatment.

In the future, the approach to management of childhood WD should ideally be in a multidisciplinary setting, involving hepatologists, neurologists and psychologists/psychiatrists.

Contributors IvM, MF and DK planned, researched and wrote the main body of the article. EW planned, researched and wrote the neurology section of the article. IvM and DK edited and finalised the various drafts to produce the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. No data are available.

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