Published in final edited form as:
Lancet Neurol. 2015 January ; 14(1): 103–113. doi:10.1016/S1474-4422(14)70190-5.

Wilson's disease and other neurological copper disorders.

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Summary

The classic copper metabolism disorder, Wilson disease (WD), was first defined in 1912. Both early onset presentations in infancy and late onset manifestations in adults > 70 years are now well recognized. Modern biochemical and genetic prevalence studies suggest that WD may be considerably more common than previously appreciated. Early diagnosis of WD is crucial to ensure that patients can be started on adequate treatment but uncertainty remains about the best possible choice of medication. Direct genetic testing for *ATP7B* mutations is increasingly available to confirm the clinical diagnosis of WD. WD needs to be differentiated from other conditions that present clinically with hepatolenticular degeneration or share biochemical abnormalities with WD, such as reduced serum cerulo plasmin levels. Disordered copper metabolism is also implied in an increasing number of other neurological conditions, including a subtype of axonal neuropathy due to *ATP7A* mutations, and the common late-onset neurodegenerative disorders Alzheimer's disease and Parkinson's disease.

Introduction

2012 saw the centenary of Samuel Alexander Kinnier Wilson's seminal publication entitled "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver".[1] Wilson noticed several key features of this condition, namely its hereditary nature, the co-occurrence of liver cirrhosis with neurological deficits, and the predominantly

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Conflicts of interest:
OB - none
KHW – none
SGK – none.

extrapyramidal nature of these signs and symptoms. The discovery of increased copper levels in the brain and liver of Wilson disease (WD) patients led to the introduction of British antilewisite (BAL) and later penicillamineas the first chelating agents for WD.[3] Remarkable progress has been made since, most notably the discovery of *ATP7B* as the causative WD gene and introduction of other chelating as well as non-chelating agents for its treatment. This review will focus on recent advances in our understanding of WD. Particular emphasis is given to clinically relevant aspects such as the latest molecular genetic advances in WD, our improved understanding of the clinical presentation, diagnostic guidelines and an up-to-date discussion of the complicated treatment issues in this disorder. In addition, we will describe clinically relevant aspects of other copper disorders (several of which have only recently been discovered), distinguish them from other "heavy metal" diseases, and summarize the evidence of disturbed copper metabolism in the common neurodegenerative disorders Alzheimer's disease (AD) and Parkinson's disease (PD). Basic aspects of normal copper metabolism and the molecular mechanisms of the different copper transport diseases are summarized in Figure 1.

Genetics

WD is a monogenic, autosomal recessively inherited condition. The causative gene *ATP7B* encodes a copper-transporting P-type ATPase.[4–6] More than 500 ATP7B mutations have now been identified (http://www.wilsondisease.med.ualberta.ca/database.asp). Most of these are missense mutations, small deletions/insertions in the coding region, or splice junction mutations. Less common genetic mechanisms, including whole exon deletions, promoter region mutations, concurrent presence of three pathogenic alterations, and monogenic disomy, have also been observed by us and others but are comparatively rare.[7, 8] *ATP7B* mutation "hot spots" exist but vary considerably among different populations.[9] The point mutation H1069Q is the most common *ATP7B* mutation in patients from Central, Eastern and Northern Europe and 50–80% of WD patients from these countries carry at least one H1069Q allele.[9] Table 1 summarizes common *ATP7B* mutations in different populations.

Mutations resulting in completely absent or non-functional ATP7B protein activity are associated with early onset, typically hepatic, severe WD; these mutations are comparatively rare.[10, 11] Systematic attempts to establish firm genotype-phenotype correlations for other, more common ATP7B mutations have largely failed.[12, 13] An association between particular point mutations such as H1069Q and the late onset neurological presentation of WD was suggested but not confirmed in independent cohorts.[13–15] The lack of genotype-phenotype correlations, the clinical variability and the variable penetrance suggest the presence of modifier genes that determine an individual's level of copper tolerance or copper storage capacity. Genetic modifiers such as the presence of an E4 allele of apolipoprotein E (ApoE) or polymorphisms in the methylenetetrahydrofolate reductase gene (*MTHFR*) may contribute to age of WD onset but these studies await confirmation in larger, independent populations.[16, 17]

At the cellular level, the functional consequences of pathogenic ATP7B amino acid substitutions vary greatly even when substitutions are in the same functional domain.[18] Increased intracellular copper levels lead to oxidative stress and free radical formation as

well as mitochondrial dysfunction arising independently of oxidative stress. The combined effects results in cell death in hepatic and brain tissue as well as other organs.[19, 20]

Prevalence

The widely cited prevalence figure of 1:30,000 for WD with a heterozygous *ATP7B* mutation carrier frequency of 1:90 was estimated in 1984 and thus predates the identification of *ATP7B* as the causative WD gene. This prevalence estimate was at least partially based on assumptions and has been questioned.[21] More recent mass screening studies undertaken in East Asia suggested a considerably higher prevalence of WD (1:1,500 – 1:3,000) based on ceruloplasmin (CP) level measurements in large cohorts.[22, 23] We have recently completed the first genetic prevalence study of WD in the UK. The entire *ATP7B* coding region and adjacent splice sites were sequenced in 1,000 apparently healthy neonatal controls. Our data suggested an unexpectedly high rate (approximately 1 in 40) of *ATP7B* heterozygote mutation carriers, predicting a 1:7,000 prevalence for WD in the UK population.[7] The prevalence of WD can be considerably higher still in isolated populations.[24] The marked discrepancy between our calculated genetic prevalence data for WD (if extrapolated, suggesting approximately 9,000 current cases of WD in the UK) and the considerably lower number of clinically diagnosed WD patients is likely to be at least partially due to reduced penetrance of *ATP7B* mutations. However, our study also raises concerns that WD may still be unrecognized in a substantial proportion of affected individuals. Late diagnosis is the most common cause of death in WD.[25]

Clinical manifestations

Neurological symptoms in WD typically begin in the second or third decade.[26] While only 46/1223 (3.8%) WD patients in one large cohort became symptomatic beyond 40 years of age, approximately 2/3 of these had neurological symptoms.[27] Late onset with WD manifesting> 70 years of age is also well documented.[28] Thus, the diagnosis of WD should never be excluded because a patient is “too old”. Conversely, WD with onset in early infancy has also been reported, the youngest age of onset being 9 months.[29] However, all children diagnosed in early infancy with genetically confirmed WD presented with hepatic symptoms; it is currently unclear whether WD should also be considered in infants who present with neurological impairment at such a young age. Pediatric neurologists should nevertheless be aware of unusual presentations of WD in childhood such as spasmodic muscle cramps and myopathy.[30]

The frequency of distinct neurological features of WD such as dystonia or parkinsonism varies widely in different case series. The presence of classical “wing-beating tremor” or “flapping tremor” in combination with dysarthria strongly suggests the diagnosis of WD. However, any of the other, more common forms of tremor such as rest, action, or intention tremor can occur as well. The most common form of tremor in WD is an irregular, and somewhat jerky, dystonic tremor. Dystonia is present in at least a third of all patients with a neurological presentation of WD and can be generalized, segmental, multifocal or focal.[31] Isolated cervical dystonia is nevertheless unlikely to be due to WD.[32] Dysarthria is frequently combined with slow tongue movements andorofacial dyskinesias including the

"risussardonicus" describing involuntary grimacing with the mouth open and the upper lip contracted. Slowness of movement and other neurological features typically observed in Parkinson's disease such as hypomimia, shuffling gait, impaired fine finger movements and foot tapping are further typical features. The presence of three distinct neurological presentations of WD has been suggested, namely 1) a dystonic syndrome, 2) an ataxic syndrome and 3) a parkinsonian syndrome. However, the considerable majority of WD patients will present with a combination of these features.[26, 33] Furthermore, certain neurological features such as (dystonic) action tremor or the inability to walk heel-to-toe due to marked lower limb dystonia may be misinterpreted as cerebellar impairment with gait and limb ataxia. Pyramidal features such as pathologically brisk deep tendon reflexes can be present but paralysis is rare. The presence of sensory impairment makes the diagnosis of WD highly unlikely. Seizures also may be the presenting symptom of WD, can occur at any stage of the illness and might indeed be more common after treatment has been initiated.[34, 35] Vertical smooth pursuit has been reported to be abnormal in 85% of WD patients with neurological features on formal testing with electro-oculography but vision itself remains normal.[36]

Psychiatric symptoms can occur in both untreated and treated WD patients.[37, 38] According to one recent literature review, 20% will have seen a psychiatrist before a formal diagnosis of WD was reached. The average time between the onset of psychiatric symptoms and the diagnosis of WD was 864 days for WD patients in whom psychiatric symptoms preceded neurological or hepatic involvement.[38] The most common psychiatric features are abnormal behaviour (typically increased irritability or disinhibition), personality changes, anxiety and depression. Psychosis is considerably less common. A history of jaundice, a positive family history of neuropsychiatric disease and increased sensitivity to neuroleptics can be diagnostic clues for WD in such patients.[39] Cognitive impairment may be global in patients with advanced, untreated WD but is typically limited to impaired executive function involving fronto-striatal circuits in treated WD with preservation of verbal intelligence and episodic memory.[40] Attention deficits can be found in symptomatic and asymptomatic WD patients.[41]

It is beyond the scope of this manuscript to review other, non-neurological presentations of WD, in particular the hepatic presentation, in detail but neurologists need to be aware of the fact that WD can present both with acute liver failure or chronic liver disease which may clinically be indistinguishable from other hepatic conditions. Neurologists also need to consider the diagnosis of WD if asked to see a patient with "unexplained hepatic encephalopathy". Conversely, the absence of clinical or biochemical evidence of liver disease does not exclude WD.

Diagnostic Investigations

A scoring system for WD diagnosis was developed by attendees at an international meeting in Leipzig, Germany in 2001 (Table 1). This approach collates biochemical, clinical and molecular genetic data from individual patients to provide a quantitative score, and is now included in the European Association for the Study of the Liver (EASL) clinical practice guidelines for Wilson disease.[42] Typically, the presence of Kayser-Fleischer rings (KFR)

(Figure 2) and serum ceruloplasmin (CP) < 10 mg/dl are sufficient to establish the diagnosis. Intermediate CP levels with CP below the normal range but above 0.5 mg/dl may indicate that the patient is a heterozygote ATP7B mutation carrier. However, KFR are absent in about half of all hepatic patients.[43] It can easily be missed on bedside testing, especially in patients with dark eyes. Referral to ophthalmology for slit-lamp examination should therefore be considered in most suspected cases. Occasionally, KFR can be present in other hepatic conditions such as primary biliary cirrhosis. CP levels can also be low in other conditions such as hepatic insufficiency due to advanced liver disease. Of note, the oral contraceptive pill can elevate CP levels to the normal range. False normal CP values can also result from inflammatory conditions since CP is an acute phase reactant. Laboratory findings that further support the diagnosis of WD include low serum copper levels, elevated hepatic transaminase levels, aminoaciduria, and hemolytic anemia. However transaminase levels may be normal in WD patients who present with neurological symptoms.[43] Analysis of 24 hr urine copper excretion in urine is an easily performed and important diagnostic test for WD. Acid-washed (copper-free) collection containers should be used. Urinary copper excretion greater than 100 μg per 24 hr in the absence of cholestatic liver disease is typical for WD. Even values greater than 40 μg/24 hr (0.64 μmol/24 hr) are suggestive of WD in asymptomatic children.[44] Inmost centres, the D-penicillamine “challenge” has only been validated in paediatric patients. 500 mg of penicillamine is administered orally after collecting baseline 24-hour urine. The D-penicillamine dose is repeated after 12 hours, the midpoint of the second 24-hour urine collection. A several-fold increase in copper excretion in the second collection is highly suggestive of WD.[45] A liver biopsy for measurement of hepatic copper may rarely be indicated in patients with the neurological presentation of WD in whom other investigations are ambiguous. Hepatic copper values greater than 250 micrograms per gram of dry weight (normal 20–50) are characteristic of WD. Intermediate values (50–200 microgram per gram of dry weight liver tissue) suggest heterozygote *ATP7B* mutation carrier status.[46] Incorporation of ^{64} copper into serum ceruloplasmin is a further highly specific diagnostic test. The appearance of radioactive copper in the serum is measured after an oral load, with most WD patients only incorporating very little ^{64} copper into CP. The usefulness of this radio-copper incorporation test is limited due to its restricted availability.

Crucially, family screening, including assessment of both clinically unaffected siblings and their parents for WD is mandatory to detect presymptomatic WD (see also treatment section). As a minimum, this should include clinical assessment including examination for KFR, copper and ceruloplasmin studies. Ideally, genetic testing should also be performed on all first-degree relatives of affected individuals.

Imaging

Magnetic resonance imaging (MRI) abnormalities were present in all 56 WD patients included in a large case series of 100 patients with early-onset extrapyramidal disorders. However, the well-known “face of the giant panda” sign was only detected in 14.3%. Other abnormalities such as tectal plate hyperintensity (75%), central pontinemyelinolysis-like abnormalities (62.5%) and concurrent signal changes in basal ganglia, thalamus and brain stem (55.3%) were considerably more common (Figure 3).[47] Rarely, WD can result in

diffuse white matter abnormalities and thus needs to be considered as a possible etiology of diffuse leukencephalopathy.[46] Other imaging techniques such as 7 Tesla MRI, T2 weighted imaging, MR spectroscopy, transcranial brain parenchyma sonography (TCS) or single-photon emission tomography (SPECT) are currently only being used in research.[49–52] Importantly, MRI brain abnormalities can completely regress after successful treatment.[53]

Genetic testing

In the past, the utility of direct genetic testing for *ATP7B* mutations was limited by the comparatively low rate of mutation detection and slow turnaround time.[54] However, direct genetic testing is likely to play an increasingly important role in the confirmation of the clinical diagnosis of WD due to improved techniques and a steady reduction in the costs of genetic investigations. We have recently shown that two pathogenic *ATP7B* mutations can be detected in 98% of all patients with clinically confirmed WD if the entire *ATP7B* coding region and adjacent splice sites are sequenced.[7] Both promoter mutations and gene dosage problems such as whole exon deletions are rare and therefore do not need to be included in a routine genetic workup of *ATP7B*. In many populations, a step-wise approach, initially focusing on sequence analysis of *ATP7B* mutation hotspots, is likely to save costs and time. Sequence analysis of *ATP7B* can be particularly helpful in patients with unusual presentations.[30] We and others have reported the presence of WD in two or more generations of the same family, reflecting “pseudo-dominant” inheritance, presumably due to the comparatively high prevalence rate of *ATP7B* mutations in the general population.[7, 55] Thus, the diagnosis of WD cannot be excluded on clinical grounds simply because the family history misleadingly suggests an autosomal dominantly inherited gene defect.

Treatment

Drug treatment

Medical therapy in WD must be lifelong since abnormal copper accumulation cannot be controlled by a low copper diet. A theoretical, sequential treatment concept differentiates between the initial, acute de-coppering therapy and the subsequent maintenance therapy. This concept takes into account that, after the initial more aggressive treatment phase, a reduced dose or less toxic medical approach might be sufficient to maintain normal copper homeostasis. Adjustment of the maintenance treatment dose also helps to prevent overtreatment that can result in copper deficiency.[56]

In general, treatment options include the copper chelators (D-penicillamine, trientine and tetrathiomolybdate) and/or zinc salts. While chelating agents bind copper directly in blood and tissues and facilitate its excretion, zinc interferes with the intestinal uptake of copper. The latter mechanism involves induction of metallothionein synthesis in intestinal epithelial cells; increased metallothionein synthesis leads to preferential binding of dietary copper to metallothionein in these intestinal cells, which are shed subsequently. Thus, zinc impedes further copper accumulation but has lower de-coppering potential and thus less potential to mobilize copper from tissues already overloaded.

Since prospective controlled comparative studies are limited, we will discuss the different medical treatment approaches in the context of recent retrospective studies. These studies

emphasize the difficulty of choosing the appropriate de-coppering agent, especially in a WD patient with neurologic symptoms, and demand a careful monitoring of risks associated with the respective drugs.

A recent retrospective European multicenter study analyzed the treatment outcome in 405 patients receiving D-penicillamine or trientine for at least 6 months.[57] While chelation therapy – irrespective of the particular drug – led to hepatic improvement in > 90% of patients, the response rates for symptomatic neurologic patients were considerably less favourable. After 4 years of therapy, an improvement of neurological symptoms was only seen in 88/143 (62%) patients. The failure to respond to chelation therapy in 38% of these WD patients with neurological presentation may reflect irreversible brain damage.

Paradoxical worsening of the clinical neurological presentation is reported in up to 20% of patients after initiation of chelation therapy with either D-penicillamine or trientine. The mechanism of this neurologic deterioration is not fully understood, but appears to be related to dosage since a high starting dose could increase the risk of rapid chelator-induced paradoxical worsening. To mechanistically understand this phenomenon, a concept of different copper pools has emerged that differentiates between high-affinity bound copper (bound to CP, the main copper-containing protein in blood) and so called “free copper” not bound to CP. A plausible mechanism explaining the neurologic deterioration could be over-mobilization of copper by chelator therapy leading to an elevated free copper pool with resultant cell toxicity. This hypothesis is supported by a landmark study by Brewer et al. that demonstrated an association between an unfavourable neurologic course and elevated levels of the “free” copper pool. Recent animal studies also demonstrated an increase of low-affinity bound copper in the CNS associated with enhanced oxidative stress following initiation of D-penicillamine therapy in the toxic milk mouse model. [58,59] Thus, a flexible dose increase adjusted to control the free copper pool may help to avoid neurological deterioration. Also worrisome is the observation of long term neurological worsening in 10/143 patients on chelation therapy, which raises questions about the efficacy of D-penicillamine and trientine to control WD-related brain involvement.[57]

In our view, the currently available data do not allow a strong recommendation of one chelating agent above the other. We suggest that the respective advantages and disadvantages of D-penicillamine and trientine are discussed with the patient and a decision is then made based on their individual needs and the respective side-effect profile.

A different chelating agent, tetrathiomolybdate (TTM) may be a promising alternative as it appears to be superior in reducing the circulating free copper pool.[60] TTM is fast acting and can restore normal copper balance within several weeks compared to the several months required for other copper chelators or zinc. However, clinical experience with this drug remains limited; the ammonium formulation has proven too unstable for routine clinical use. Of note, a bis-choline formulation of TTM has recently become available on a named patient basis in the EU and US. Further studies, especially long-term follow-up studies including direct comparisons with the traditional copper chelating agents are needed to determine the efficacy of TTM for routine clinical practice.

Due to the different mode of action, treatment with zinc salts is less often associated with paradoxical deterioration after initiation of therapy, but these potential advantages may be outweighed by overall lower treatment efficacy. With zinc, a comparatively long time (4–6 months) is needed to generate negative copper balance when used in the initial stages of treatment. This might account for reports of non-response or worsening under zinc therapy.[43] Nonetheless, zinc used as the primary treatment in asymptomatic WD or neurologically affected WD patients has shown long-term outcomes comparable to D-penicillamine therapy in some centres.[61,62] A major concern in WD patients on zinc monotherapy is control of the hepatic disease. We observed a hepatic non-response with increased liver enzymes and urinary copper excretion in 14/88 patients, reflecting insufficient treatment efficacy under zinc monotherapy.[43] Others have reported development of new liver disease during zinc monotherapy in 20% of patients with initial neurological presentation.[62]

The debate between those favoring chelating agents and those favoring zinc will only be settled if a prospective, randomized controlled trial is conducted to compare both treatments directly. In our view, patients with newly diagnosed neurological WD should be started on chelation therapy to ensure adequate “de-coppering” within an acceptable time frame. Patients (and physicians) need to be warned that it can easily take 1–3 years until a patient with neurological WD can be switched to maintenance therapy. Close monitoring of clinical and laboratory parameters may be more important than the actual choice between D-penicillamine, trientine, or zinc for subsequent maintenance therapy. We typically aim for Cu < 0.6 mg/24 h urine (collected OFF medication) in WD patients on pencillamine as maintenance therapy.

The safety profile of all oral de-coppering agents appears acceptable, although data on long-term use of D-penicillamine in a recent series indicated that 99/313 (31.6%) of patients discontinued D-penicillamine treatments due to significant side-effects. These included nephrotoxicity, hematological abnormalities, and elastosisperforansserpiginosa (usually involving the neck and axillae).[57] Adverse events associated with trientine and TTM use include bone marrow toxicity, whereas zinc therapy is often associated with gastrointestinal discomfort. Independent of the chosen medical regimen, non-adherence or discontinuation of medical therapy due to non-compliance is associated with the risk of intractable hepatic decompensation.[63,64]

Accordingly, easy to follow drug regimens – especially once daily schemes, as for TTM or those under investigation for trientine (clinical.trials.gov: NCT01472874), could result in improved outcomes. Those clinicians who favour a combination of zinc and a copper chelator need to be aware of a possible interaction between the drugs.

Lifelong presymptomatic treatment for WD in clinically unaffected relatives is mandatory and can consist of either chelating agents or zinc.[42]

Monitoring of WD patients

Even with asymptomatic or stable disease monitoring intervals of 6 months seem reasonable to ensure clinical and biochemical response and to identify adverse events in a timely

fashion[42]. Laboratory testing should include serum parameters of copper metabolism, urinary copper as well as liver function tests. Very low urinary copper levels and pancytopenia may indicate an overtreatment. Like in any other chronic liver disease ultrasound screening for hepatocellular carcinoma is justified. However, newly developed hepatic or neurological symptoms, or reoccurance of clinical findings like KFRs are “red flags” and indicate a non-controlled copper state.

Liver transplantation

Liver transplantation is a rare consideration in WD since the condition is usually responsive to medical therapy. Liver transplantation corrects the hepatic genotype and restores copper excretion capacity and should be considered in WD patients presenting with acute liver failure (fulminant WD) or decompensated (chronic) cirrhosis due to WD. The role of liver transplantation as a treatment option for patients presenting with severe neurologic symptoms remains controversial. [65–67]

Symptomatic treatment

Concurrent with the findings of non-improvement of neurologic patients despite adequate de-coppering therapy (see above), approximately 1/3 of all neurological WD patients are on symptomatic treatment, typically botolinum toxin injections for dystonia or primidone for tremor.[68] Thalamotomy or deep brain stimulation may also be beneficial in carefully selected cases of otherwise treatment-resistant tremor or patients who are non-compliant with chelation therapy.[69]

Other copper transport disorders and related diseases

Menkes disease and variants

Mutations in *ATP7A* are typically detected in Menkes disease, an X-linked recessive disorder of impaired copper absorption.[70] Menkes disease typically presents in males at 2–3 months of age with loss of previously obtained developmental milestones and the onset of hypotonia, seizures, and failure to thrive. White matter abnormalities on MRI reflect impaired myelination. Diffuse brain atrophy, ventriculomegaly, and tortuosity of the cerebral vasculature are also present. Without early treatment, death within the first several years of life is typical. Current management is limited to parenteral copper replacement, which can be highly successful depending on *ATP7A* mutation type and the timing of treatment.[71] Adeno-associated virus-mediated gene addition is emerging as a prospective treatment, especially relevant for subjects with severe *ATP7A* defects.[72]

The occipital horn syndrome is a milder allelic variant of Menkes disease, so-named in reference to the pathognomonic wedge-shaped calcifications that form within the trapezius and sternocleidomastoid muscles at their attachments to the occipital bone in affected individuals. This protuberance can be palpated in some patients and is demonstrable radiographically on lateral and Towne’s view skull X-rays, or appropriate sagittal CT or MRI images. Occipital horn syndrome shares the hair and connective tissue abnormalities of classical Menkes disease. Because the neurological phenotype in this variant is mild (slight generalized muscle weakness, and dysautonomia including syncope, orthostatic

hypotension, and chronic diarrhea), affected individuals often escape detection until mid-childhood or later.[70]

More recently, a third *ATP7A* phenotype, distal motor neuropathy without overt copper metabolic abnormalities, was found in association with mutations in the ATP7A copper transporter.[73] This newly recognized *ATP7A* allelic variant involves progressive distal motor neuropathy with minimal or no sensory symptoms. Signs include distal muscle weakness with curled fingers, foot deformities and diminished deep tendon reflexes. In 12 affected individuals from the two families in which this phenotype was first discovered, age of onset ranged from 5 to 50 years, with a median of 14 years. This wide range of age of onset is similar to that seen in patients with WD, implying that environmental and/or other genetic influences may be relevant. When fully progressed, the *ATP7A*-related motor neuron phenotype is reminiscent of type 2 Charcot-Marie-Tooth disease (CMT2).[74]

Neurophysiological studies indicate reduced compound motor amplitudes with normal conduction velocities. Patients with the two specific *ATP7A* mutations (T994I, P1386S) associated with this phenotype manifest neither the severe infantile central neurological deficits observed in Menkes disease, nor signs of autonomic dysfunction as seen in occipital horn syndrome, nor the hair and connective tissue abnormalities found in both conditions, nor any of the typical biochemical features of those well characterized phenotypes. These facts highlight the distinction between this isolated distal motor neuropathy and the syndromes previously associated with *ATP7A* mutations. The CMT2-like phenotype is due to altered intracellular localization of the ATP7A protein and interaction with p97/VCP, a ubiquitin-selective chaperone.[75] Of note, autosomal dominantly inherited P97/VCP mutations have been found to be one cause of familial a myotrophic lateral sclerosis.[76]

MEDNIK syndrome

Two additional newly recognized copper metabolism disorders conditions are inherited as autosomal recessive traits. MEDNIK represents an acronym for the syndromic constellation of mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratodermia. The causative gene for MEDNIK is *AP1S1* which encodes sigma 1A, a small subunit of the adaptor protein complex-1 (AP1). AP1 normally mediates intracellular trafficking of transmembrane proteins.[77] Mutations in *AP1S1* affect systemic copper metabolism by perturbing copper ATPase trafficking, resulting in hypocupremia, hypoceruloplasminemia, and hepatic copper accumulation as in WD. Liver disease in MEDNIK patients may improve dramatically in response to therapy with zinc.[78]

Huppke-Brendl syndrome

Low serum copper and CP levels are also characteristic in infants and children with homozygous or compound heterozygous mutations in *SLC33A1,* which encodes the acetyl CoA transporter, AT-1.[79] AT-1 is normally required for acetylation of many gangliosides and glycoproteins and perhaps the two copper ATPases, as well. AT-1 deficiency causes reduced CP secretion *in vitro*, suggesting that post-translational acetylation of this glycoprotein is necessary. The biochemical phenotype is but one aspect of this condition, now called Huppke-Brendl syndrome, a lethal autosomal-recessive disorder of congenital

cataracts, hearing loss, and severe developmental delay. Cerebral MRI in affected subjects shows pronounced cerebellar hypoplasia and hypomyelination, reminiscent of Menkes disease.[74]

Manganese storage disorder

A newly identified manganese storage disorder, due to autosomal recessively inherited mutations in the manganese transporter gene *SLC30A10,* has been described as the "new Wilson disease".[80] Patients with this disorder typically develop generalized dystonia in childhood and adolescence (2–14 years) or asymmetrical parkinsonism and early postural instability in adulthood (47 and 57 years for the two cases reported with this presentation so far).[81,82] Of note, patients with this condition also develop hepatic cirrhosis and thus mirror the "hepatolenticular degeneration" first observed in WD. Typical laboratory findings include polycythemia, depleted iron stores with low ferritin and high total iron binding capacity as well as increased manganese levels in serum and basal ganglia hyperintensities on T1 brain MRI imaging.[80] The treatment of choice for these patients is repeated intravenous CaNa2-EDTA infusions, leading to a marked increase in urinary manganese excretion. Both parkinsonian and dystonic features can dramatically approve after such infusions but successful treatment response may depend on early diagnosis and initiation of treatment.[80,83]

Aceruloplasminemia

Aceruloplasminemia belongs to a group of neurodegenerative disorders with brain iron accumulation (NBIA). It may be confused with WD due to very low or absent serum CP (protein) levels in patients who may present with symptoms and brain imaging findings suggestive of WD.[84] It is properly considered a disorder of iron (not copper) metabolism resulting from autosomal recessively inherited mutations in the *ceruloplasmin* gene. While CP contains copper, this protein acts as an iron oxidase. Loss of CP ferroxidase activity leads to iron accumulation in the pancreas, liver and brain. In contrast, iron accumulation does not occur in WD.[85] Clinically, aceruloplasminemia is characterized by the triad of retinal degeneration, diabetes mellitus and neurological symptoms which are present in about 2/3 of all cases.[86] Neurologically, patients typically manifest in the fifth and six decade of life with ataxia (71%), involuntary movements including dystonia, chorea and tremor (64%) or cognitive dysfunction (60%), parkinsonism (20%) is present in approx. 20%.[86] Of note, heterozygote *ceruloplasmin* mutation carriers may also become clinically manifest.[87] Diabetes (typically type 2) can precede the neurological symptoms by several decades.[88] In addition to low or absent CP, patients with aceruloplasminemia typically show elevated serum ferritin, decreased serum iron, microcytic anemia, and low serum copper with normal urinary copper levels. Brain imaging reveals hypointense basal ganglia, dentate nucleus and thalamic signal changes. Attempts to treat aceruloplasminemia with the iron chelator desferrioxamine have given inconsistent and largely disappointing results.[86]

Copper and other neurodegenerative disorders

Copper and CP have been implicated in the pathogenesis of both Alzheimer's disease (AD) and Parkinson's disease (PD).[89] Copper enhances dimerization of amyloid precursor protein

(APP) and promotes amyloid-β (Aβ) production.[90] Recent meta-analyses reported an increase of free (non-CP bound) copper levels in serum and cerebrospinal fluid of AD patients.[91,92] Furthermore, higher free copper levels in serum are associated with unfavourable evolution of cognitive function in AD.[93] Copper critically regulates low-density lipoprotein receptor-related protein-1 mediated Aβ clearance across the blood-brain barrier in normal mice. In a mouse model of AD, copper added to the drinking water already influenced Aβ production and neuroinflammation at low copper levels.[94] An association between *ATP7B* haplotypes and AD has been reported in one candidate gene study.[95] In contrast, a recent meta-analysis of genome-wide association (GWAS) studies in AD did not identify the *ATP7B* locus as an AD risk locus.[96]

The synucleins are a family of redox-active copper binding proteins.[97] Alpha-synuclein has two copper binding sites, and increased formation of alpha-synuclein aggregation is the direct consequence of the formation of an alpha-synuclein-copper complex.[98] However, copper levels are decreased in both the serum and the substantia nigra of PD patients, making direct implication of copper in the pathogenesis of PD unlikely.[99,100] In contrast, iron levels are increased in PD brain tissue.[89] As mentioned above, the copper-containing protein CP has ferroxidase activity and decreased CP levels lead to increased iron deposition in the substantia nigra (SN) in PD and lower CP levels may be associated with earlier onset of this condition.[101,102] Levels of oxidized CP with reduced ferroxidase activity are increased in the CSF and there is an ~ 80% loss of CP ferroxidase activity in the SN of PD patients.[103, 104] Of note, peripheral infusion of CP attenuated neurodegeneration and nigral iron elevation in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of PD.[103] Thus, CP-upregulation may be a promising disease-modifying strategy for PD.

Outlook

Recent studies have firmly established the usefulness of direct genetic testing for the diagnosis of WD, raised concerns about the possibility of a considerably higher prevalence of WD than previously accepted, and highlighted the advantages and disadvantages of the currently available treatment for WD. The phenotype for other copper disorders such as those due to *ATP7A* mutations has been widened and new early onset disorders of copper metabolism have been identified. However, little progress has been made to address at least some of the remaining key issues, including the risk of neurological deterioration after initiation of therapy and the lack of improvement in about a 1/3 of all patients with neurological WD. Preclinical assessment of experimental therapies for the CNS manifestation of WD is complicated by the current absence of a neurological phenotype in all classical ATP7B mutant or knockout rodent animal models of WD.[105] A new vertebrate animal model of WD with clear symptomatic brain involvement would therefore be very valuable. Nonetheless, it is plausible to hypothesize that the combination of standard WD drugs with antioxidants, mitochondrial rescue agents, or compounds to lowers phingomyelinase activity – reported to be increased in WD - may improve neurological outcomes.[106] Clinical trials designed to assess these hypotheses are needed. Such trials will be facilitated by the recent development of a validated neurological rating scale for WD.[107]

Gene therapy approaches represent novel and potentially effective management strategies for WD.[108,109] Liver-directed adeno-associated viral gene therapy could be further assessed in currently available animal models but questions regarding likely costs and acceptable benefit vs risk profile remain. Gene or cell-based therapies offer the potential to simplify WD management by reducing reliance on daily use of therapeutic compounds. Finally, assessment of new as well as existing treatment strategies by prospective randomized clinical trials would be facilitated by the identification of WD biomarkers.[110]

Acknowledgments

This work was supported by the Sheffield Hospitals Charity grant 7884 (OB), and projects Z01 HD008768 and Z01 HD008892 from the Intramural Research Program, National Institutes of Health.

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Search Strategy and selection criteria

References cited in this Review were identified through PubMed searches using the search terms “Wilson disease”, “Wilson’s disease”, “Menkes disease”, “Aceruloplasminemia”, “copper and Parkinson’s disease”, “copper and Alzheimer’s disease”, “MEDNIK”, “ATP7B”, “ATP7A”, “AP1S1”, “SLC33A1”, “SLC30A10” from January 2009 to June 2014. Articles were identified through searches of the reference lists of the articles found with the above cited search terms and of the authors’ own files. All references used in this Review were published in English, and were selected according to originality and relevance to the content of this review.

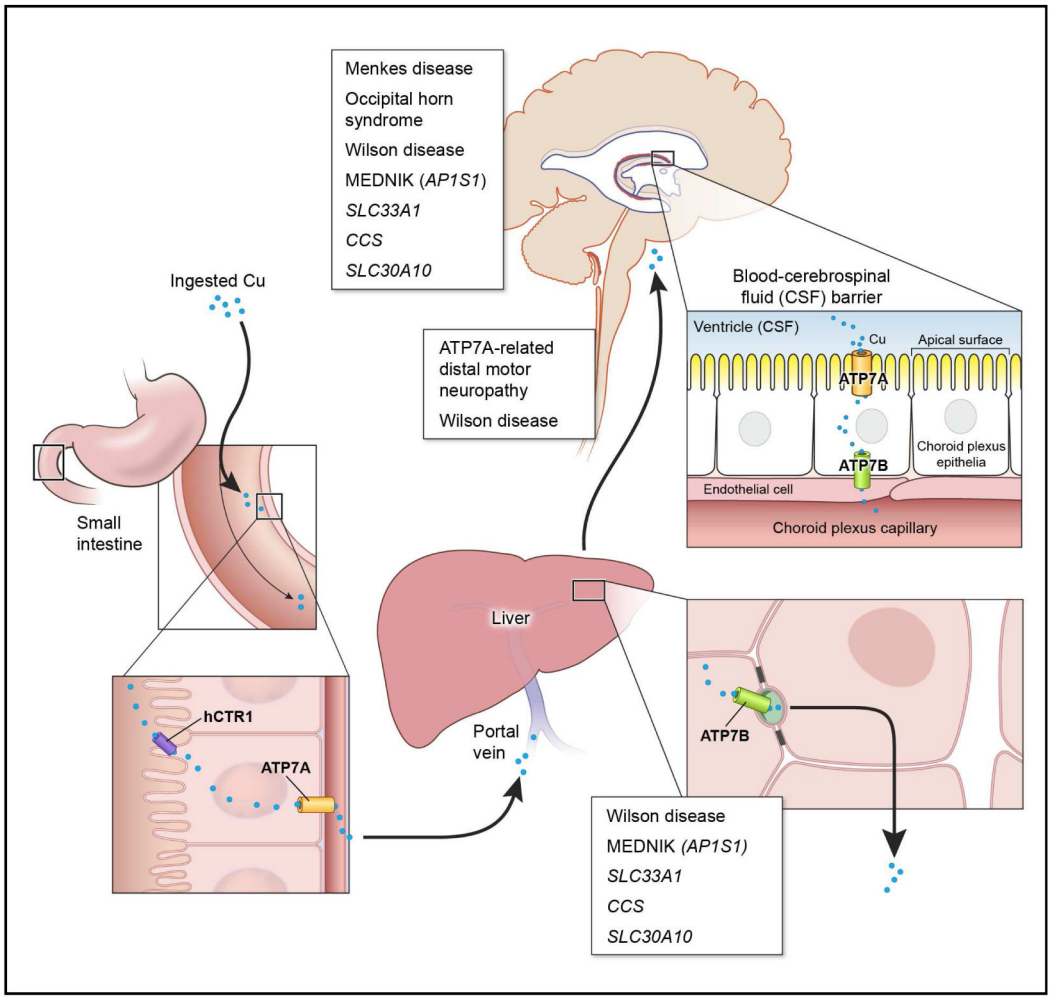

Figure 1.

Normal copper metabolism and the molecular mechanisms of copper transport disease. Copper absorption occurs in the small intestine via enterocyte uptake by hCTR1, and passage into the blood mediated by ATP7A at the basolateral aspect of duodenal epithelia. Copper is conveyed to the liver via the portal circulation and excess removed by excretion into the bile at the apical aspect of hepatocytes, a process impaired by mutations in *ATP7B*. Copper diseases of the liver also involve the *AP1S1* gene implicated in MEDNIK syndrome, an acetyl CoA transporter, *SLC33A1*, and a cytosolic copper chaperone, *CCS*. See text for details. Mutations in a manganese transporter, *SLC30A10*, produce hepatic cirrhosis due to manganese accumulation that can mimic Wilson disease. *ATP7A* and *ATP7B* are believed to mediate copper entry and exodus, respectively, at the blood-CSF (cerebrospinal fluid) barrier of choroid plexus epithelia. Brain copper deficiency (Menkes disease) or excess (Wilson disease), respectively, result from mutations in these essential copper transporters. The central nervous system is also affected by alterations of *AP1S1*, *SLC33A1*, *CCS*, and *SLC30A10*. Isolated motor neuron degeneration occurs in association with unique *ATP7A* missense mutations affecting axonal trafficking, and sensory peripheral neuropathy can be a component of Wilson disease.

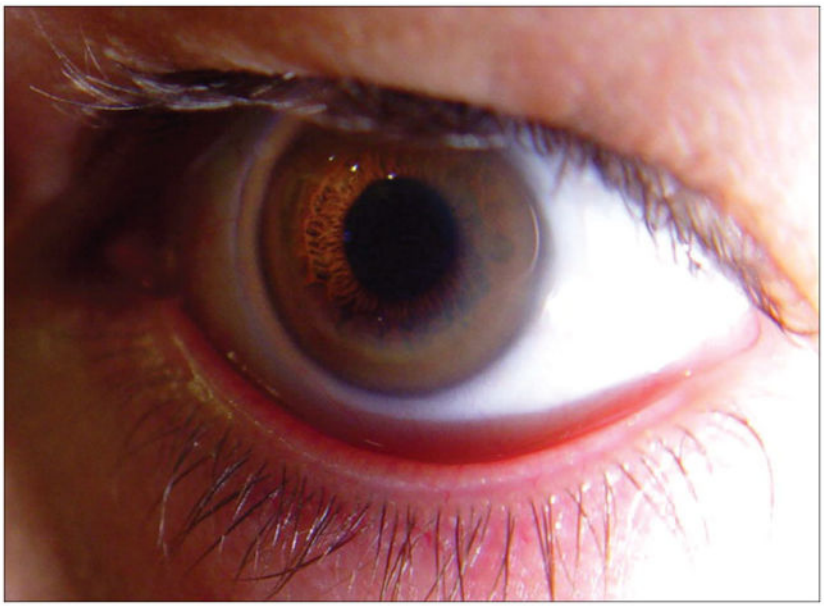

Figure 2.

Kayser Fleischer ring with copper deposition in Descemet's membrane, leading to brown discolouration at the outer margin of the cornea (Reference to be added – Aftab et al., Lancet 2007 - and comment to be added "with permission by Elsevier")

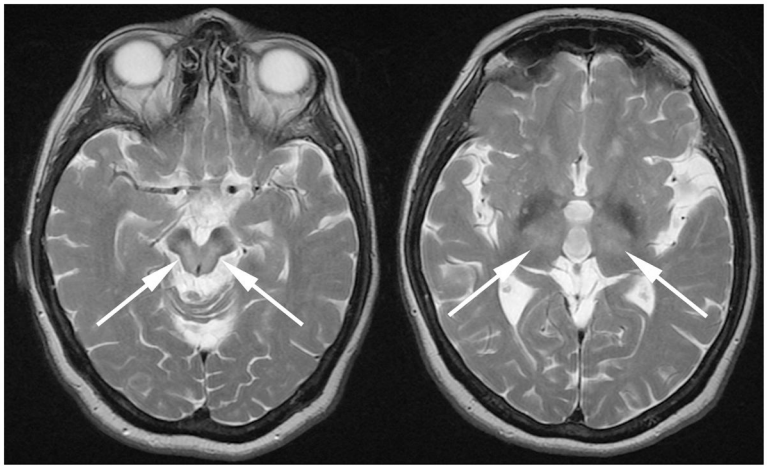

Figure 3.

Two representative T2-weighted axial brain MR images showing on the left (solid white arrows) with symmetrical T2-w hyperintense lesions in the tectal midbrain on the left and in the ventromedial thalami and posterior limbs of the internal capsule on the right (kindly provided by Dr. M. Pham, Department of Neuroradiology, Heidelberg University Hospital, Germany).

Table 1

Common *ATP7B* mutations in different populations.

Population	DNA nucleotide change	Protein amino acid change	Exon	Frequency	Other common mutations
Asian	c.2333G>T	p.Arg778Leu	8	30–50%	c.2871delC
European	c.3207C>A	p.His1069Gln	14	35–45%	c.2299insG c.1934T>G
India	c.813C>A	p.Cys271Stop	2	~20%	c.3305T>C c.2975C>T
Arabia	c.4196A> G	p.Gln1399Arg	21	~30%	

Table 2

Scoring system for Wilson disease diagnosis developed by attendees at the international WD meeting in Leipzig, Germany in 2001.

Typical clinical symptoms and signs		**Other tests**	
Kayser Fleischer rings		**Liver copper** (in absence of cholestasis)	
Present	2	>5xULN (>250μg/g)	2
Absent	0	50–250μg/g	1
Neurologic symptoms**		Normal (<50μg/g)	−1
Severe	2	Rhodanine positive granules*	1
Mild	1	**Urinary copper** (in absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1–2x ULN	1
Normal (>0.2g/l)	0	>2x ULN	2
0.1–0.2g/l	1	Normal, but >5xULN after D-pen	2
<0.1g/l	2	**Mutation Analysis**	
Hemolyticanemia		On both chromosomes detected	4
Present	1	On 1 chromosome detected	1
Absent	0	No mutations detected	0
TOTAL SCORE		Evaluation:	
4 or more		**Diagnosis established**	
3		**Diagnosis possible, more test needed**	
2 or less		**Diagnosis very unlikely**	

* if no quantitative liver copper available,

** or typical abnormalities on brain MRI