

Wilson's disease: A review of what we have learned

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Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: All authors declare they have no conflict of interest.

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Received: June 14, 2015

Peer-review started: June 15, 2015

First decision: August 4, 2015

Revised: November 5, 2015

Accepted: December 1, 2015

Article in press: December 2, 2015

Published online: December 18, 2015

Abstract

Wilson's disease (WD), which results from the defective ATP7B protein product, is characterized by impaired copper metabolism and its clinical consequences vary from an asymptomatic state to fulminant hepatic failure, chronic liver disease with or without cirrhosis, neurological, and psychiatric manifestations. A high grade of suspicion is warranted to not miss cases of WD, especially less florid cases with only mild elevation of transaminases, or isolated neuropsychiatric involvement. Screening in first and second relatives of index cases is mandatory, and treatment must commence upon establishment of diagnosis. Treatment strategies include chelators such as D-penicillamine and trientine, while zinc salts act as inductors of methallothioneins, which favor a negative copper balance and a reduction of free plasmatic copper. As an orphan disease, research is lacking in this field, especially regarding therapeutic strategies which are associated with better patient compliance and which could eventually also reverse established injury.

Key words: Wilson's disease; Wilson disease; Chelating agents; Penicillamine; Zinc; Copper; Orphan disease; Liver transplantation

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Core tip: A century after its initial description by Kinnear Wilson in 1912, knowledge on diagnosis and management of Wilson's disease reflect its prevalence as a rare disease, largely deriving from experts' opinions and the use of pharmacological agents without the rigorous randomized clinical trials that are the mainstay. Prompt recognition and treatment are paramount and life-saving.

Rodriguez-Castro KI, Hevia-Urrutia FJ, Sturniolo GC. Wilson's

disease: A review of what we have learned. *World J Hepatol* 2015; 7(29): 2859-2870 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i29/2859.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i29.2859>

INTRODUCTION

Initially described by Kinnear Wilson^[1] in 1912, Wilson's disease (WD, or Wilson disease), is the clinical condition resulting from mutations in the chromosome 13q14 in the region coding for the protein product *ATP7B*, and occurs in a sporadic fashion as well as inherited as an autosomal recessive disease. Homozygous, or, more commonly, compound heterozygous mutations lead to defective incorporation of copper into apo-ceruloplasmin and the subsequent formation of holoceruloplasmin, hampering the normal excretion of copper into bile. Consequences of this defect are the impaired copper metabolism and consequent copper intoxication. With a shorter half-life than that of holoceruloplasmin, circulating apoceruloplasmin (ceruloplasmin) are abnormally low, albeit the gene responsible for this protein, localized on chromosome 3, is intact^[2], providing one of the most important clinical diagnostic tools for WD. Copper overload, and actually free copper as the main acting element, exerts its toxicity through two main mechanisms: Direct oxidative stress, with lipid peroxidation of membranes, DNA, and mitochondria, as well as due to unregulated apoptosis leading to cell death from copper-induced changes in the anti-apoptotic protein, X-linked inhibitor of apoptosis, and its loss of inhibitory control of caspase-3^[3]. It is now known that it is not the accumulation of copper itself what is deleterious to the organism, but rather free copper in the blood, which determines copper intoxication, as opposed to ceruloplasmin-bound copper. Thus, the old paradigm of eliminating copper stores as the therapeutic objective has given way to the concept of normalizing free copper concentrations in the bloodstream^[4].

It should be stated that much of the knowledge that has accumulated in the decades following the first description of the disease, as well as the mainstays of treatment, derive greatly from experts' opinions and some from anecdotal experiences, and not on adequately designed randomized comparative studies.

EPIDEMIOLOGY

The prevalence of WD, a rare disease, is similar in most world regions, corresponding to approximately 0.5 cases per 100000 inhabitants^[5,6], or the most common figure 30 cases per million, with a gene frequency of 0.56% and a carrier frequency of 1 in 90^[7]. Nevertheless, the disease is much less uncommon in certain areas/countries, with certain mutations being described more frequently in specific populations. Over 500 mutations have been found so far^[8], and the lower number of actual clinically manifest cases with respect to the fre-

quency of allele carriers in the population, probably reflect the reduced penetrance of mutations. The most common mutations include His1069Glu (H1069Q) in Europe and North America^[9], Arg778Leu in South Korea^[10], Japan^[11] and China^[12], 2007del7 in Iceland^[13], and Met645Arg in Spain^[14]. The disease is most frequent in Germany (2.5/100000 inhabitants), Japan (3.3/100000 inhabitants)^[11] and Austria (3.0/100000) inhabitants^[15]. The country with the highest incidence in the world, however, is Costa Rica (4.9/100000 inhabitants; see below section on perspectives from a high-incidence country), possibly due to elevated degree of consanguinity and a possible founder effect, the most frequent mutant being Asn 1270 Ser^[16-18], previously described only in Sicilian, Lebanese and Turkish populations. The other region of the world with a very high incidence (estimated 1/10000-1/7000) is Sardinia^[19,20], where a well-documented founder mutation (-441/-427del) is highly prevalent (67%) and all other mutations are present with a relative frequency below 10%^[19,21,22].

CLINICAL MANIFESTATIONS

Although the form of the disease initially described was predominantly neurological^[1], the disease manifestations can be pleomorphic, and although the correlation mutation-predominant manifestation has been elusive^[23,24], clinical forms of the disease tend to cluster and wide geographical differences exist^[25]. Thus, WD may be predominantly hepatic, neurological or psychiatric, and manifestations of disease may range from an asymptomatic state to life-threatening fulminant hepatic failure^[26-30]. In Costa Rica, the majority of WD patients exhibit a liver-predominant disease, with more than 5% presenting as fulminant Wilson disease (FW)^[17].

Liver involvement spans from asymptomatic disease with transaminase elevation, to acute hepatitis, acute-on-chronic liver failure, and cirrhosis. Liberation of copper into the bloodstream causes Coomb's negative hemolytic anemia, with transient episodes of low-grade hemolysis and jaundice^[31,32]. Neurological manifestations can be categorized as: (1) an akinetic-rigid syndrome similar to Parkinson's disease; (2) pseudosclerosis dominated by tremor; (3) ataxia; and (4) a dystonic syndrome, which often leads to severe contractures^[33,34]. Neuropsychiatric symptoms and signs, including decrease in scholastic performance, hand-eye discoordination, and behavioral changes may foretell a more florid neurological presentation^[35]. Other findings include drooling, spasticity, chorea, athetosis, myoclonus, micrographia, dyslalia, hypomimia, and dysarthria^[35,36]. Ocular manifestations include the Kayser-Fleischer ring and sunflower cataracts in the lens, deposition of copper in the Descemet's membrane in the first case, and in the anterior and posterior capsule of the lens, sparing epithelial and cortical cells, in the latter^[37,38]. Although Kayser-Fleischer rings are very common in WD, especially in patients with neurological forms of the disease, sunflower

cataracts are more rarely observed. Sunflower cataracts associated with Kayser-Fleischer rings in WD patients were first described in 1922 by Seimerling and Oloff, who observed a striking similarity between these lesions and those induced by a copper-containing foreign body lodged in the eye. Both manifestations may resolve with continued therapy^[39]. Small fiber peripheral neuropathy involving the corneal nerve plexus^[40], as well as neuronal degeneration involving the retina have also been described^[41], using novel techniques such as corneal confocal microscopy and spectral domain optical coherence tomography, respectively. Psychiatric abnormalities, which may be present before hepatic or neurological signs in up to one third of patients^[42], include decreased academic performance or personality changes, sexual exhibitionism, impulsiveness, labile mood, inappropriate behavior, depression, paranoia, and schizophrenia, leading also to suicide in a discrete number of cases^[15,33,43,44]. Other manifestations of disease may include renal abnormalities such as hypercalciuria, nephrocalcinosis, nephrolithiasis, and aminoaciduria, cardiomyopathy with arrhythmias, autonomous nervous alterations, gigantism, hyperparathyroidism, osteoarthritis, pathological fractures and pancreatitis^[42,45].

DIAGNOSIS

The working party at the 8th International Meeting on Wilson disease held in Leipzig (2001)^[26,42] proposed a diagnostic score for diagnosing WD. The fundamental diagnostic elements include: (1) serum ceruloplasmin, which is typically decreased by 50% of the lower normal value, but may be elevated - and thus lead to a false negative result in inflammatory states, as an acute phase reactant; (2) twenty-four hours urinary copper excretion, which is typically greater than 100 mcg/24 h in adults and greater than 40 mcg/24 h in children; (3) serum free copper, which is typically greater than 200 mcg/L; (4) hepatic copper, which is typically greater than 250 mcg/g dry weight; and (5) the presence of Kayser-Fleischer rings on slit-lamp examination, which however may be absent in up to 50% of patients with hepatic WD, may be absent in most asymptomatic siblings, and may be present in other hepatic diseases such as primary biliary cirrhosis. In contrast, Kayser-Fleischer rings are present almost invariably in neurological WD^[37]. Although oftentimes most criteria of the Leipzig score are met^[26], the alteration of at least one copper metabolism test with low ceruloplasmin in levels in the presence of clinical manifestations is enough to establish the diagnosis of WD. The advent of genetic testing did not provide the expected diagnostic yield, due to the existence of more than 500 mutants, and the laborious and expensive nature of genetic testing^[46]. Moreover, most patients are mixed (compound) heterozygotes, and even more so, no mutation has been identified in approximately 17% of confirmed WD cases^[47]. However, genetic testing might prove to be very useful, and molecular techniques allow for a rapid diagnosis in a

substantial part of patients with prevalent mutations. Furthermore, genetic testing is especially useful in screening relatives of the index patient, upon determination of his/her mutant.

Other simple diagnostic options include the relative exchangeable copper, defined by the ratio of serum exchangeable copper (CuEXC)/total serum copper (CuT) > 18.5%^[48]. The simplest test, however, remains the serum copper/ceruloplasmin ratio ($\mu\text{g/dL}$), which if is greater than 2 determines the existence of WD, and if < 1 determines a healthy subject or a heterozygote^[49]. Although the 24 h urine test is used widely, it is not practical and may be difficult to collect for patients. A 6 h copper urine test after challenge with D-penicillamine is being proposed by our group, which provides diagnostic rapidity, and good accuracy with the cutoff level of 118 mcg Cu/6 h as diagnostic for WD^[50]. This test has not yet been universally validated yet, however, and has not been standardized for routine diagnosis, but rather represents a valid tool under certain circumstances, especially in patients with acute on chronic presentation with rapid clinical deterioration. Moreover, the future holds promising new techniques such as tandem mass spectrometry as a diagnostic tool, which although not yet widely available, may be used as a confirmatory test to diagnose WD in newborns, allowing a very fast measurement of several metabolites in different biological specimens^[51].

As prompt diagnosis is crucial in order to initiate treatment hopefully in the early, asymptomatic stage of the disease and not when liver decompensation or advanced neurological irreversible damage have already ensued, family screening is warranted. In this scenario, the best approach is to complete copper studies in first- and second-degree relatives of the index case.

TREATMENT

Treatment should ideally commence upon diagnosis in pre-symptomatic subjects (when testing is performed as part of screening for affected family members), or in symptomatic subjects, immediately after prompt diagnosis. If treatment is initiated opportunely, deterioration can be prevented and life expectancy can be comparable to subjects without the disease^[52,53]. Prognosis for WD patients is excellent provided compliance to therapy is adequate. On the contrary, the natural course of the disease is characterized almost inevitably by progressive, relentless deterioration leading to death due to liver or neurological disease^[54]. Discontinuation of treatment may be catastrophic, placing the patient at high risk of FW, and with a high toll on mortality, as in a study where 8 of 11 patients who suspended treatment died an average of 2.6 years after treatment cessation^[55].

The objectives of treatment, therefore, are to prevent appearance of symptoms in asymptomatic subjects, prevent clinical deterioration in affected subjects, and can also be life-saving in cases of acute-on-chronic hepatitis. Treatment principles in WD include the esta-

blishment of a certain diagnosis, since the treatment is lifelong, as well as the monitoring of compliance, early detection of complications, and integral management including early neuropsychiatric screening/evaluation and physiotherapy, as required.

It is recommended that asymptomatic patients be treated with zinc salts or with chelators at a lower dosage than that used for symptomatic disease. In contrast, symptomatic patients should be treated with chelators or a combination of chelators plus zinc, while patients with acute-on-chronic liver failure or those with end-stage liver disease unresponsive to medical therapy should be considered urgently for liver transplantation. In order to determine the adherence to therapy, its effectiveness, and the eventual development of side effects, lifelong monitoring is warranted.

Treatment is based on the removal of copper excess by chelating agents such as penicillamine, trientine^[55], or tetrathiomolybdate^[56,57] or by blocking the intestinal copper absorption with zinc salts^[58], with the ultimate goal of normalizing free plasmatic copper. Being WD a rare disease^[59], pharmacological agents to treat it belong to the group of orphan drugs^[60], and have not been developed through a rigorous process like most drugs, for which information on pharmacokinetics and pharmacodynamics is available before their establishment as treatment and their marketing. Rather, pharmacological agents in WD originated from the desperate need to treat an otherwise lethal disease and even derive from knowledge in other fields, like chemistry and veterinary medicine, as in the case of tetrathiomolybdate. An exception is represented by zinc acetate, for which formal preclinical and clinical trials were conducted prior to its release as a treatment agent for WD, as requested by the American Food and Drug Administration for approval of an alternative zinc salt^[61]. The continued use of these agents through the years, however, has permitted a body of evidence and experience to be accumulated regarding these drugs' effectiveness and adverse effects. The orphan drugs presently used for the treatment of WD, with no registered active clinical trials, research projects or networks^[60] are penicillamine D (or D-penicillamine) (Cuprimine, Cupripen, Cilamin, Trolovol, Orpha number ORPHA34567), zinc acetate (Galzin, Wilzin, Orpha number ORPHA56897), Trientinedihydrochloride (Metalite, Syprine, Orpha number ORPHA24924), and Ammonium tetrathiomolybdate (Orpha number ORPHA137334), designation granted to the last agent by the European Commission in 2008^[62].

D-penicillamine

D-penicillamine, introduced in 1956 as the first oral agent for treating WD^[63], chelates not only copper, but other metals as well. In fact, the initial racemic mixture that was available required the co-administration with pyridoxine^[32], to avoid deficit of this vitamin, although supplementation with pyridoxine (25-50 mg daily) is still recommended. This drug favors urinary excretion of copper, but it also induces the endogenous intracellular

chelator metallothionein^[64,65], favoring reduced absorption by elimination in feces. As D-penicillamine has some immunosuppressant properties, it was in fact initially used to treat rheumatoid arthritis^[66]. Moreover, this agent's interference with collagen cross-linking has several consequences^[67,68], including impaired or delayed wound healing, but also potential benefic effects in preventing, delaying, or ameliorating hepatic fibrosis. This last effect was not demonstrated in a histopathological study in which fibrosis progression occurred in the same proportion in patients treated with zinc or with D-penicillamine^[69], although larger studies and longer follow-up is warranted to evaluate this aspect optimally. Although initial worsening of neurologic symptoms may occur in 10%-50% of patients^[53,70], it is widely used due to its low cost and considerable efficacy, although no comparative data exist to support its superiority as opposed to zinc therapy^[71].

Improvement in hepatic function may be observed as early as 2-6 mo after initiation of treatment, with improvement in hepatic synthetic function, ascites, and jaundice^[32,72]. Initial recommended dose is 250-500 mg/d, with 250 mg increments every 4-7 d to a maximum of 1-1.5 g/d in two to four divided dosages, in cases of symptomatic disease. Maintenance dose is lower: 750-1000 mg/d administered in two daily doses. In the pediatric population, the recommended dose is 20 mg/kg per day rounded off to the nearest 250 mg and distributed in two or three doses daily, reducing by 25%-30% in maintenance therapy. As food inhibits the absorption of D-penicillamine, this drug should be administered one hour before or two hours after meals^[73,74]. Adverse effects are unfortunately relatively common with the use of D-penicillamine and determine the need for discontinuation (and switching to another pharmacological treatment) in approximately 20%-30% of patients^[75]. Early adverse effects include sensitivity reactions characterized by fever and cutaneous eruptions, neutropenia or thrombocytopenia, lymphadenopathy, and proteinuria. Although in the past desensitization measures were used due to the absence of pharmacological alternatives, the occurrence of these adverse reactions warrants immediate drug suspension and switching to either trientine or zinc. Another late adverse effect of D-penicillamine which requires immediate suspension is nephrotoxicity, which is often preceded by proteinuria or the appearance of other cellular elements in the urine. Other late-onset undesirable effects of the drug include a lupus-like syndrome characterized by hematuria, proteinuria, arthralgia, and appearance of antinuclear antibodies; bone marrow toxicity with severe thrombocytopenia and even aplasia may occur, while dermatologic alterations such as elastosis perforans serpiginosa, progeria, pemphigus, lichen planus, and aphthous stomatitis may occur^[67,76]. Hepatic iron accumulation has been demonstrated to occur with prolonged use of D-penicillamine, as opposed to therapy with zinc, which avoids copper absorption, and hepcidin might play a role in altered iron metabolism in WD^[77].

Neurological damage, in some cases irreversible, may be induced by massive and sudden free copper elevation following therapy with D-penicillamine and other potent chelators^[78]; neurological worsening has in fact been linked with spikes in free copper, induced by chelators including D-penicillamine^[79,80]. The mechanism behind neurological worsening is the mobilization of important amounts of free copper, which together with an increase in malanodialdehyde and a reduction in glutathione, lead to cellular damage^[81]. Moreover, due to its effects on collagen formation and thus on wound healing, D-penicillamine must be suspended (and therapy changed to zinc or trientine) between 2 to 3 mo before planned surgery.

Trientine

A chelator of several metals including copper, zinc, and iron, trientine was developed and introduced in 1969 as an alternative for patients intolerant to D-penicillamine and favors urinary excretion of copper^[82,83]. Although its elevated cost might hamper its use as an initial medication, and although clinical information available is limited only to uncontrolled studies, this agent possesses a good safety profile and is efficacious, offering the possibility of use as alternative to other pharmacological agents or as initial therapy, even in cases of decompensated liver disease^[84]. Albeit worsening of neurological symptoms has been reported to occur, this phenomenon seems to occur less frequently than with D-penicillamine. Cases of neurotoxicity have been reported^[85], however, and a clinical trial found that trientine led to initial neurological deterioration in approximately 26% of treated patients^[86]. Co-administration with iron should be avoided, since the resulting complex may induce toxicity. Copper deficiency induced by trientine through overtreatment can result in reversible sideroblastic anemia due to marrow copper deficiency^[87] and iron overload in livers of patients with WD, similar to that observed for D-penicillamine. Recommended dose is 750-1500 mg/d in two or three divided doses, while maintenance dose is 750-1000 mg/d in two or three divided doses. In the pediatric population, dosing is 20 mg/kg per day, rounded off to the nearest 250 mg, and should be administered in two or three divided doses. Similar to D-penicillamine, trientine should be administered either one hour before or two hours after meals, as food inhibits its absorption. Another particular aspect is that trientine must be kept refrigerated. Adverse effects include dyspepsia, anemia caused by iron deficiency, muscle cramps and spasms, and dystonia, the last being difficult to exclude as manifestations of the disease itself^[88].

Zinc

Initially its chloride salt, followed by its sulfate salt, zinc was first used in the early 1960s to treat WD but was kept unrecognized until 1978^[89]. Zinc acetate is regarded to have a better gastric tolerance. However, in terms of efficacy, there is no difference between zinc

salts^[90]. Its mechanism of action is different from the above mentioned agents, in that it induces enterocyte metallothionein, an endogenous chelator of metals, thus favoring copper entrapment into enterocytes and its elimination in the feces with the normal shedding of intestinal cells^[61,91]. Furthermore, zinc may also act beneficially by inducing intra-hepatic metallothionein, potentially providing further hepato-protection^[92]. Another possible mechanism of action of zinc is the inhibition of lipid peroxidation and the increase of available glutathione within hepatocytes, reducing oxidative damage^[93]. This drug has demonstrated to be efficacious in slowly creating a negative copper balance, and although initially it was favored only as maintenance therapy or in asymptomatic subjects^[94], it is increasingly and successfully being used as first-line therapy as well^[4,95,96]. As the deleterious effect of copper are associated with its free form in blood, induction of metallothionein and its binding of free copper by zinc results in an efficacious therapy, achieving normalization of free copper levels. Recommended dosing in milligrams of elemental zinc is 150 mg/d divided in three doses. In the pediatric population dosing is 75 mg/d divided in three doses. As well as with the other pharmacological drugs in the armamentarium for treating WD, food interferes with absorption, which is why this drug must be administered at least one hour before or two hours after meals. Whenever the therapeutic decision to switch from chelators to zinc is made, it should be noted that since the maximum induction of intestinal metalloproteins occurs three weeks after the initiation of zinc, the chelator should be continued for this period of time, administered at least one hour before or after zinc. Adverse effects of zinc are fortunately few and not life-threatening, including gastric irritation, which can improve with time, alcohol intolerance, headaches, increase in perspiration, transient elevation of plasmatic lipase, amylase and alkaline phosphatase, and sideroblastic anemia, the latter of which can indicate excessive copper removal, with copper deficiency^[97].

Since neurological worsening might be induced with the use of potent chelators, it has been proposed^[98], and it has been the experience of our groups, that the optimal therapeutic approach in patients with severe neurological impairment is to commence treatment with zinc, which acts not by rapid mobilization of copper, but by blockage of copper absorption both from food as well as from endogenously secreted copper, creating a consistent negative copper balance without inducing an intense and sudden copper redistribution^[78]. Not only as initial therapy in cases of severe neurologic involvement, but also as an alternative agent after discontinuing chelators, zinc therapy has been proven to favor improvement and even resolution of neurological damage in WD^[99].

Although not standardized, combined therapy, with the administration of either D-penicillamine and zinc, or trientine and zinc, at widely spaced intervals during the day, is a valid strategy that has yielded good results^[100]. Both the EASL and the AASLD guidelines recommend including a chelating agent in the initial treatment of

symptomatic patients (D-penicillamine or trientine), although trientine may be better tolerated^[32,42]. Likewise, according to these guidelines, maintenance therapy can be ensued with reduced doses of either chelating agent or with zinc.

Diet

Elevated amounts of copper are naturally found in numerous food products, including chocolate, nuts, mushrooms, crustaceans, soy, and gelatin, and although dietary restriction of copper-rich foodstuffs is by no means sufficient therapy for WD^[101], its importance should not be overlooked as part of WD management. Moreover, the use of cooking utensils containing copper is discouraged, and in order for tap water coming from copper pipes to be sufficiently safe for consumption, it must be left running for a few minutes^[97].

PHARMACOLOGICAL TREATMENT MONITORING

Adequate compliance to therapy is key in the management of patients with WD^[94]. Being a lifelong disease, frequently diagnosed in the pediatric age, and requirement daily intake of one or more pharmacological agents, oftentimes two or three times daily, adherence can sometimes be an issue, and can lead to life-threatening deterioration of clinical conditions. Monitoring should be performed at least every six months, especially in adolescents, in whom non-adherent behavior has been documented in spite monitoring^[102]. Monitoring intervals should be shorter for patients who initiate therapy, patients who are switched to another type of medication, cases in whom non-compliance is suspected, or patients in whom worsening occurs in spite of treatment.

Monitoring of treatment with all agents includes liver function tests, which should tend to normalize within a variable period of several months. With either D-penicillamine or trientine, plasmatic non-ceruloplasmin bound copper values should exceed 25 µg/dL at the start of therapy and should lie between 15-25 µg/dL during maintenance therapy. At the start of therapy, 24 h urinary copper excretion should be between 500 and 1000 µg/24 h (or from 300 to 1000 with trientine), and should lie between 200-500 µg/24 h during maintenance therapy. Conversely, monitoring of patients on zinc therapy must ensure a reduction in urinary copper excretion (initially below 100 µg/24, and from 30-80 µg/24 h on maintenance therapy), with a normalization off non-ceruloplasmin-bound copper (initially above 25 µg/dL, but 15-25 µg/dL on maintenance therapy). Additionally, urinary zinc excretion (which should be above 1.5-2 g/d) indicates adequate compliance to therapy^[3,32].

It is important to look out for overtreatment, which presents with neutropenia and anemia, due to failed iron mobilization, with transaminase elevation due to increased hepatic iron, accompanied by increased

ferritin. In these cases, non-ceruloplasmin copper is typically lower than 15 µg/dL, and urinary copper is reduced with respect to the patient's previous values^[3]. Temporary discontinuation of therapy, or switching from a chelating agent to zinc, with close observation, is warranted, followed by reintroduction of therapy at a reduced dose^[32].

LIVER TRANSPLANTATION

Liver transplantation is the recommended therapy for patients with fulminant hepatitis, or in those with relentless progression of hepatic dysfunction despite drug therapy, and survival rates are only very slightly inferior to those after transplant for other indications^[103-105]. Liver transplantation corrects the underlying hepatic metabolic defect in WD^[106], and is one of the few indications for liver transplantation in which there is no risk of recurrence, unless in the unfortunate and improbable hypothesis of receiving a graft from an undiagnosed WD. With the availability of effective treatment, liver transplantation is clearly not indicated to treat the metabolic defect, but rather as a life-saving procedure in cases of advanced cirrhosis or fulminant hepatic failure. In a study analyzing UNOS results on 170 children and 400 adults who underwent liver transplantation for FW or end-stage liver disease in the United States between 1987 and 2008, Arnon *et al.*^[102] found that both one- and five-year survival rates were similar between children and adults (90.1% and 89% vs 88.3% and 86%, respectively, $P = 0.53, 0.34$). Moreover, both adults and children transplanted for chronic liver disease had better long term survival than patients transplanted for FW, although the difference was not statistically significant^[107]. Neurological, and especially psychiatric^[108] involvement may show little improvement with transplantation, however^[27]. In a multicenter Italian study, 37 cases of patients who underwent liver transplantation, 8 for FW and 29 for WD-related chronic liver disease, were analyzed, demonstrating decreased survival in patients who previous to transplant had neuropsychiatric manifestations, in spite of neurological improvement after transplantation^[103]. Improvement in neurological symptoms, without a negative effect on survival, has been reported however, in smaller series^[109,110]. Thus, caution must be employed in decision making regarding listing for liver transplantation in patients with severe neuropsychiatric involvement. Moreover, liver transplantation for sole neuropsychiatric disease is currently not recommended.

ALTERNATIVE TREATMENTS

Ammonium tetrathiomolybdate

Tetrathiomolybdate, another copper-chelating drug with antiangiogenic properties^[111], derives from experience in the veterinary field, where this agent has been used to treat copper-poisoning^[106,112]. Its mechanism of action is chelating copper and also inducing intestinal

metalloproteins, increasing both copper elimination in the urine and in the feces^[86]. Administered with meals, this agent forms a complex with copper and protein in the gut, inhibiting copper uptake; when administered between meals, it binds plasmatic copper^[113-115]. Although not yet approved by the American Food and Drug Association, it has been approved for use in WD in Europe since 2008. In spite of the reduced clinical experience available, it seems this agent is safe and efficacious, especially in patients with severe neurological manifestations^[54,57,111,115]. In a randomized, double-blind study analyzing patients with neurologic WD, treatment with trientine and tetrathiomolybdate were compared against each other. The authors found that neurological deterioration occurred in 6 of 23 patients in the trientine treatment arm vs 1 of 25 patients in the tetrathiomolybdate arm^[86]. Adverse effects include elevation of transaminases and bone marrow suppression^[116].

Vitamin E

Vitamin E, a powerful antioxidant, may be used as adjunctive treatment, especially in the scenario of liver failure. Moreover, low levels of this vitamin have been demonstrated in patients with WD, providing further rationale for its supplementation^[117-119]. Nevertheless, no randomized controlled studies offer solid evidence for its use.

TREATMENT IN SPECIAL CONDITIONS

Fulminant hepatic failure

Prompt recognition and establishment of diagnosis is the first, crucial step in the management of acute liver failure; timely diagnosis in these circumstances is especially critical, and high suspicion for this entity must be raised in the presence of a fulminant hepatitis (in most cases in the absence of previous symptoms), Coombs negative hemolytic anemia, transaminase elevation (AST/ALT > 2.2), alkaline phosphatase/total bilirubin < 4, and an increase in serum total copper levels. The diagnosis of WD is even likelier if this presentation occurs in young females between 11 and 25 years of age, coinciding with puberty, as FW has been described more frequently in this subgroup of patients.

Treatment in this setting is life-saving, and the best option is offered by liver transplantation^[120,121]. Determination of which patients will likely not survive without a liver transplant is key to deciding urgent placement with high priority in the waiting list for liver transplant in countries/regions where this resource is available. The prognostic score developed by Nazer *et al.*^[122] incorporates serum bilirubin, aspartate aminotransferase, and prothrombin time, and patients with a score of 7 or more had fatal outcome. Dhawan *et al.*^[123] recently modified this score (revised King's score), with the addition of leucocyte count and INR instead of prothrombin time, with a newly established cutoff of 10 points which determines a breaking point in survival

without liver transplantation. The specific prognostic index revised Wilson prognostic index represents a valid tool for assessing these critically ill patients^[121,122].

As bridging therapies to liver transplantation, or as an alternative altogether in regions where liver transplantation is not possible, strategies such as rapid plasma exchange^[124,125] via any method such as plasmapheresis^[126], hemofiltration^[127,128], albumin dialysis^[129], or exchange transfusion, may be successfully used to lower circulating copper levels, renal protection from copper-mediated tubular damage, and reduce hemolysis^[130]. Albeit some degree of improvement has been reported, the need for liver transplantation has not been obviated in numerous cases, although successful treatment without transplantation has been reported^[131]. The molecular adsorbent recycling system ultrafiltration device, which combines ion exchange with albumin dialysis might provide some therapeutic efficacy in this setting, achieving copper removal and clinical stabilization, that might constitute a bridge for liver transplantation^[132-135].

Pregnancy

Treatment must be maintained during all the duration of pregnancy; acute liver failure has been reported as a result of therapy discontinuation during pregnancy^[136]. Penicillamine, trientine, and zinc salts have been successfully used to treat pregnant WD patients, with satisfactory outcomes for both mother and fetus. However, there are reports of teratogenicity associated with D-penicillamine in both animals^[137] as well as human beings^[138], and although it is not clear if trientine is effectively teratogenic in humans, its teratogenicity has been reported in animals^[139]. Although there have been reports of birth defects during treatment for WD, the rarity of this disease makes it difficult to establish a true increased risk in this population. The risk of decompensation in cases of discontinuation of therapy clearly outweighs any possible risk to the fetus. Thus, the best treatment option during pregnancy and breastfeeding is zinc, with adequate protection of the mother's as well as the fetus' health^[140]. Dosing should be unaltered for zinc salts, but reduction (20%-50%) is warranted for D-penicillamine and trientine. Monitoring of liver function tests during each trimester is recommended.

PERSPECTIVES FROM TWO HIGH-INCIDENCE COUNTRIES: ITALY AND COSTA RICA

In an Italian study analyzing 35 patients with WD, with a mean follow-up of 15 years, hepatic presentation was the dominant clinical manifestation, with 65.7% of patients with hepatic form and 34.3% a combination of neurologic and hepatic involvement. After initial treatment with D-penicillamine (23/35 patients) or zinc sulphate (12/35 patients), neurological symptoms worsened or remained stationary in 75% in patients treated with D-penicillamine, while 90% of patients

treated with zinc showed improvement in neurological symptoms, while hepatic disease improved in both treatment groups. Four patients underwent liver transplantation, and while 3 patients survived a mean of 4.6 years, one patient, who previous to the transplant had severe neurological impairment, died shortly after transplantation due to central pontinemyelinolysis^[141].

United by a possible founder effect that has been traced to Italian origins^[16,17], WD is very frequent in Costa Rica, favored by the high degree of consanguinity. In a cohort of 55 WD patients in Costa Rica, with a mean follow up of 11.59 years, for a total of 633 patient-years, mean age at diagnosis was 22.1 years, with the youngest patient being diagnosed at 3 years of age and the oldest patient at 72 years of age. Interestingly, women tended to be diagnosed at a later age than men (25.8 years vs 17.9 years, $P = 0.04$), and 41.8% of patients had at least one relative who had been diagnosed with the disease. Notably, 21 patients were asymptomatic at diagnosis (diagnosed by screening of family members), 21/55 had predominantly hepatic disease, 5/55 predominantly neurological disease, 3/55 both hepatic and psychiatric disease, 3/55 both hepatic and neurological disease, and 2/55 patients had all three possible predominant manifestations of WD: Hepatic, neurologic and psychiatric. Approximately 60% of these patients is on treatment with D-penicillamine, 8.5% on combined treatment D-penicillamine + zinc, and the remainder of patients receive either trien-tenemonotherapy, trientene + zinc, or zinc monotherapy (10.6%, respectively). Interestingly, survival was significantly different according to age at diagnosis (and start of therapy), with 97% vs 66.7% survival at 15 years for patients diagnosed before or after 30 years of age, respectively ($P < 0.01$). During the follow-up period, 2 patients underwent liver transplantation, one for FW and the other for end-stage liver disease, with excellent outcome post-transplantation (13 and 7 years' survival, respectively). Before the institution of the National Liver Transplantation program in Costa Rica, however, management of FW was successful with the use of prostaglandins (misoprostol) and high dose vitamin E in four cases^[97]. This strategy, together with copper filtering, may be life-saving and might represent a valid strategy either as a bridge to transplant or as salvage therapy in regions where liver transplantation is not an option.

CONCLUSION

Much has been learnt since the initial description of the disease, and certainly advances in the pharmacological and transplantation fields have allowed better management of patients affected by WD. However, the pharmacological armamentarium is still rudimentary, with side effects, a non-specific mechanism of action, and which constrain patients to take medication several times a day life-long. Gene therapy and hepatocyte cell transplantation are promising strategies in the treatment

of WD, although there is still a long way to go until they can be used safely and readily in humans^[142,143].

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