

Review Article

Neurologic Wilson's Disease and its Management - An Update

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Abstract

Wilson's disease is an inborn error of copper metabolism caused by mutations in the ATP7B gene. The disease has an autosomal recessive mode of inheritance and is characterized by excessive copper deposition, predominantly in the liver and brain. Clinical manifestations of neurologic Wilson's disease include variable combinations of dysarthria, dystonia, tremor, and choreoathetosis. Among neurodegenerative disorders. WD is preventable and treatable if they are diagnosed treated early. Untreated case of Wilson's disease progresses to severe neurologic disability and death, while those adequately treated have normal life spans.

The traditional treatment for WD is based on copper chelation with agents such as D-penicillamine, but use of this drug has been questioned because of reported side effects. The use of agents such as Zinec, trientine and ammonium tetrathiomolybdate has been advocated, although results of long-term trials are awaited. This review focuses on the neurologic features of Wilson's disease and treatment options.

Keywords: ceruloplasmin; dysarthria ; dystonia ; d-penicillamine ; tetrathiomolybdate

The Historical background of neurologic Wilson's disease

The landmark paper in this disease was written in 1912 by Samuel Alexander Kinnier-Wilson, an American neurologist working at The National Hospital at Queen Square in London.¹ He described a neurologic disorder associated with progressive lenticular degeneration of the brain and cirrhosis of the liver that came later to be known as Wilson's disease, or hepatolenticular degeneration. In 1952 ceruloplasmin was demonstrated to be low in Wilson's patients.² A low biliary excretion of copper was later shown to be responsible for a failure to regulate copper balance. The molecular era of medicine brought the chromosomal localization of the Wilson's disease gene to chromosome 13q14.3 and identification of the causative gene, ATP7B a copper transporting P-type transmembrane ATPase.³⁻⁵ By 1951, Cuming, Denny-Brown, and Porter described benefits of BAL in treatment of Wilson's disease.^{7,8} Description by Walshe in 1956 of the potential use of penicillamine to chelate copper in Wilson's disease.⁹ Early in the 1960s use of zinc as a decoppering agent was first undertaken by Schouwink and Hoogenrand.¹⁰⁻¹¹ Seeking an alternate to penicillamine therapy, in 1969

Walshe began using trientine and has subsequently reported its beneficial effects in those refractory to penicillamine.¹² As had been observed with zinc, molybdenum was known to induce copper deficiency in sheep. This observation eventually led Walshe, in 1986, to consider its use in Wilson's disease. The effectiveness of tetrathiomolybdate as a treatment of Wilson's disease has now been confirmed.¹³⁻¹⁶

Epidemiology

Wilson's disease appears to be typical of rare autosomal recessive diseases and it is present at a low frequency in all populations. An estimate for the disease frequency in most populations is about 17 per million, which would lead to a carrier frequency of 1 in 122.¹⁷ As with most autosomal recessive diseases, there may be pockets of excess Wilson's disease produced by founder effects, particularly if consanguinity is common in the population.¹⁸

Clinical manifestations

During early life, the patient is presymptomatic but is accumulating copper, which invariably causes subclinical liver disease. Then, between early childhood and the fifth or sixth decade of life, but with a peak incidence of around 17 years, the patient presents with hepatic, neurologic, and psychiatric manifestations.¹⁹ Those with a primarily hepatic presentation appear to have an earlier age at

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presentation than those with the primarily neurologic presentation.¹⁹⁻²⁰ Although Wilson's disease usually presents in childhood to early adulthood, a wider range of age at onset is recognized. This review deals primarily with neurologic Wilson's disease, and hepatic manifestations will be briefly considered.

Neurologic manifestations

Walshe, who introduced penicillamine, trientine, and tetrathiomolybdate therapy, stated that "no two patients are ever the same, even in a sib ship, and that there is no such thing as a typical picture of Wilson's disease."²⁷ Mean age at onset of neurologic symptoms from large case series range from about 15–21 years of age.^{20,21-25} Neurologic manifestations at initial presentation have been reported in approximately 18–68%.²⁰⁻²⁴ The main clinical categories of neurologic Wilson's disease have been variably divided by neurologic presentation and signs. The clinical categories that encompass the majority of neurologic Wilson's disease are dysarthric, dystonic, pseudosclerotic (tremor +/- dysarthria), or parkinsonian.²⁰⁻²⁵ During the course of the disease, other neurologic features such as chorea, athetosis, myoclonus, seizures, ataxia, pyramidal signs, drooling and eye movement abnormalities are also present.²¹

Table-I

Clinical presentation of neurologic Wilson's disease

	<ul style="list-style-type: none"> • Movement disorders (tremor, involuntary Neurological movements) • Drooling, dysarthria • Rigid dystonia • Pseudobulbar palsy • Dysautonomia • Migraine headaches • Insomnia • Seizures
Psychiatric	<ul style="list-style-type: none"> • Depression • Neurotic behaviours • Personality changes • Psychosis
Other systems	<ul style="list-style-type: none"> • Ocular: Kayser-Fleischer rings, sunflower cataracts • Cutaneous: lunulae ceruleae • Renal abnormalities: amino-aciduria and nephrolithiasis • Skeletal abnormalities: premature osteoporosis and arthritis • Cardiomyopathy, dysrhythmias • Pancreatitis • Hypoparathyroidism • Menstrual irregularities; infertility, repeated miscarriages

Dysarthria

Dysarthria is probably the most common neurologic manifestation of Wilson's disease. In large series that delineate dysarthria as a feature of Wilson's disease, it has been found in 85–97% of those with neurologic Wilson's disease.^{23,25} Dysarthria in Wilson's disease is most frequently of the mixed type with varying spastic, ataxic, hypokinetic, and dystonic components.^{24,25} Speech involvement is frequently concordant with the neurologic involvement in individual patients. In those with dystonia, speech frequently will have dystonic qualities with a strained or harsh quality. In those with parkinsonism, the speech quality may have hypokinetic properties. Ataxic dysarthria, with variation in word spacing and volume, is often found in association with other types of dysarthria and may be more common in those with tremor.²⁵

Dystonia

Dystonia is a common finding in Wilson's disease, reported to be present in about 11–65%.^{23-25,26,27} Dystonia can be focal, segmental, multifocal, or generalized and ranges in severity from mild to debilitating.²⁸ A common focal dystonic manifestation of Wilson's disease is the dystonic facial expression known as risus sardonicus. This type of dystonia inflicts the patient with a forced, often exaggerated smile.²⁸ Focal dystonia of the vocal cords, muscle of articulation, and swallowing frequently results in dysphonia, dysarthria, and dysphagia. Focal dystonia of the vocal cords, muscle of articulation, and swallowing can be an initial isolated feature or part of a generalized dystonia. Other focal dystonias include blepharospasm, cervical dystonia (torticollis), and writer's cramp. Dystonia, like many neurologic features of Wilson's disease, typically has a unilateral onset or predominance, but can progress to bilateral or generalized involvement. Severe dystonia may lead to extreme posturing of the trunk, neck, or extremities. The presence of dystonia has been demonstrated to correlate with MRI signal abnormalities in the putamen.^{25,28}

Tremor

Wilsonian tremor has been reported to be present in 22–55% and can occur at rest, upon assumption of a posture, or with action.^{21,23,24} Although widely known, the wing-beating tremor of Wilson's disease does not appear to be the most frequent tremor type. Early in the neurologic presentation of Wilson's disease, the tremor can be identical to the tremor of essential

tremor, with the arms most frequently involved but also involving the head and legs. It is not uncommon to encounter a tremor with multiple position- and task-dependent characteristics in an individual patient.²⁵ The kinetic tremor is most frequently in distal upper extremity, low amplitude, medium-to-high frequency tremor. The classical posture-induced wing-beating tremor, thought to be associated with lesions of the dentatorubro thalamic pathway, is a less frequently observed, lower frequency higher amplitude proximal upper extremity tremor elicited by holding the arms extended laterally or with the arms held in front with flexed elbows and palms facing downward. The wing-beating tremor is typified by increasing amplitude with increased duration of posture holding.² A unilateral isolated rest tremor is atypical in Wilson's disease. When rest tremor is present it is usually accompanied by postural and kinetic tremor, which may be more severe than the rest tremor.²³

Parkinsonism

In series in which parkinsonism has been considered as a separate symptom category, it has been reported in 19–62%.^{21,25,26} Bradykinesia, imbalance, and cogwheel rigidity are the more common parkinsonian features. Unilateral rest tremor and parkinsonism are rarely isolated clinical feature of Wilson's disease, but like idiopathic Parkinson's disease, rigidity, and tremor are typically asymmetric.

Choreoathetosis

Chorea and athetosis have been reported to occur in 6–16% of those with neurologic Wilson's disease.^{23–25,26,27} Chorea is characterized by involuntary irregular rapid movements of the face, head, trunk, and extremities that are superimposed on and interrupt normal movement. Choreic movements can be subtle and small, occurring distally in the fingers resembling piano playing movements, and may also resemble fidgetiness and be incorporated into apparently purposeful movements. In an extreme form, they can manifest as disabling uncontrolled flailing movements of the extremities, termed ballism. Chorea is frequently accompanied by athetosis, a slow writhing movement of the limbs, trunk, or neck, and this combination is referred to as choreoathetosis. When present in Wilson's disease, chorea is more common in young onset disease (16 years of age and younger), where it has been reported in 20%. In contrast, chorea was reported in only 3% of adult onset (17 years of age and older).²⁷

Ataxia

Ataxia has been reported as a common feature in Wilson's disease, present in around 30%,^{23,26} but it has not been observed or reported in other large case series.^{21,25} Cerebellar findings are rarely clinically relevant and are not found in isolation. Cerebellar involvement is associated with ocular movement abnormalities, limb incoordination impaired tandem gait and a wide based gait. Cerebellar signs, other than extremity dysmetria, such as overshoot dysmetria of the eyes and limbs, or ataxic dysarthria can be found.²⁵

Cognition

Cognitive impairment in Wilson's disease can be subtle, masked by affective involvement and recognized only in retrospect by the family or patient. When present, cognitive impairment falls into two main categories, a frontal lobe syndrome, or a subcortical dementia.^{29,30} The frontal syndrome may manifest as impulsivity, promiscuity, impaired social judgment, apathy, decreased attention, executive dysfunction with poor planning and decision making, and emotional lability, at an extreme having pseudo bulbar features. The subcortical dementia is characterized by slowness of thinking, memory loss, and executive dysfunction, without cortical signs of aphasia, apraxia, or agnosia.^{29,30} Others have suggested that cognitive involvement in Wilson's disease may be primarily related to psychiatric and motor manifestations.³²

Psychiatric features

Psychiatric manifestations may be present as often as 30–50% of the time prior to a diagnosis of Wilson's disease.^{31,32} As psychiatric symptoms are often ill defined and attributed to other causes, diagnosis of Wilson's disease is made delay during the period in which psychiatric symptoms are the sole manifestation. At diagnosis, the most common psychiatric symptom depression has been estimated to occur in 20–30% of those affected by Wilson's disease. Psychotic features do not appear to be a common manifestation of Wilson's disease.^{32,35} Psychiatric manifestations of Wilson's disease appear to be more common with neurologic involvement and are uncommon in the hepatic presentation.^{44,36}

Other neurologic features

Seizures are not an uncommon feature, occurring in approximately 6% (exceeding the general population frequency by 10-fold), are rarely the presenting feature,

and have been associated with initiation of chelating therapy.³³ Hyperreflexia, unusual stereotyped movements, and tics have also been reported.²³ Autonomic disturbances including postural hypotension, abnormal sweating, and sexual dysfunction are frequently present.

Ophthalmologic manifestations

Copper deposits in the limbus of the cornea is known as Kayser-Fleischer (KF) rings. It is seen nearly 100% of those with neurologic Wilson's disease and 50% in hepatic and presymptomatic Wilson's disease.²⁶ KF rings are typically brown to brownish-green in color and are usually more prominent in the superior and inferior regions of the cornea. KF rings are not exclusive to Wilson's disease and can uncommonly be found in other obstructive liver disease and primary biliary cirrhosis.³⁴ Sunflower cataracts are seen less commonly than KF rings, present in about 17%.³⁴ Sunflower cataract do not impair vision, cannot be seen with the unaided eye or with an ophthalmoscope and require slit-lamp evaluation for detection. With treatment, KF rings and sunflower cataract become less prominent and can gradually disappear.³⁴ Other less common ophthalmologic findings include slowing of saccades, impaired up gaze, and strabismus. The absence of nystagmus in Wilson's disease can also be diagnostically useful.³⁴

Molecular genetics and pathogenesis

The Wilson's disease gene was mapped to chromosome 13q14.3, and the causative gene identified as ATP7B.³⁻⁶ ATP7B is a 1411-amino acid, copper transporting, P-type transmembrane ATPase that is highly expressed in the liver, kidney, and

placenta.³ As a result of the mutation in the ATP7B gene, the liver is not capable of excreting excess copper into the bile, and a positive copper balance, averaging about 0.25 mg/d, is established. Copper accumulates over time, first in the liver and then in other parts of the body, such as in the brain. The damage from excessive copper appears to be oxidant in nature.^{19,39}

Wilson's disease is an autosomal recessive disease that occurs when a patient carries mutations in both copies of his/her ATP7B gene. Mutational analysis has identified over 300 different mutations throughout the ATP7B gene. A much smaller number of mutations is seen in the majority of patient, and individual mutations have been associated with different ethnic populations. The H1069Q substitution is the most common mutation in white populations representing approximately 40–60% of identified mutations.⁵⁷ The H1069Q mutation, particularly when homozygous, has been associated with a later onset neurologic disease.^{60,61} Other consistent genotype–phenotype correlations have been elusive. Because of the large number of disease-causing mutations, most patients are compound heterozygotes (have two different mutations). It is not known how the same mutation is able to cause hepatic disease in some, but neurologic in others. A combination of environmental, genetic, and epigenetic factors is likely responsible.

Diagnostic workup

The most common screening method for Wilson's disease is a blood ceruloplasmin determination,

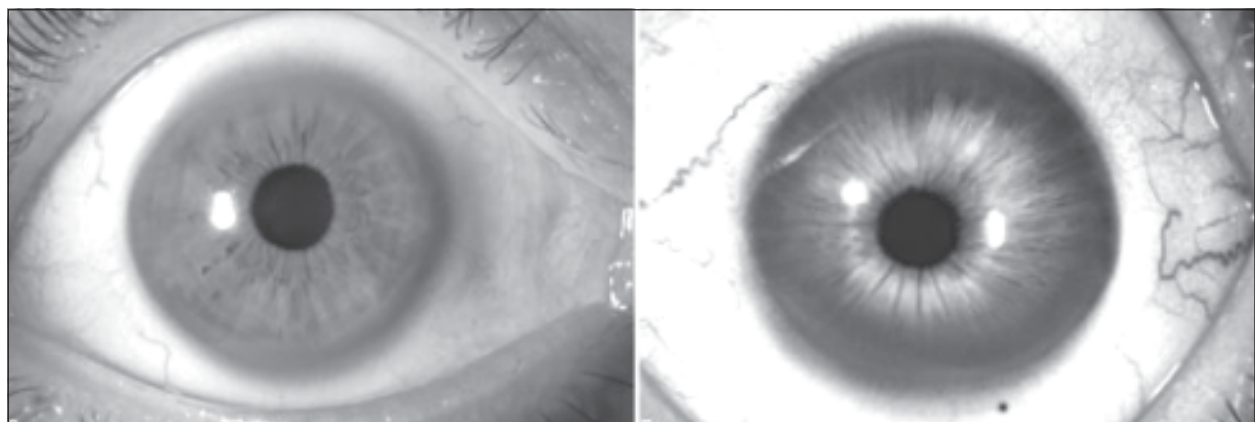


Fig-1: KF rings present in superior and inferior limbus in left picture (light), full circle involvement in right picture (brown)

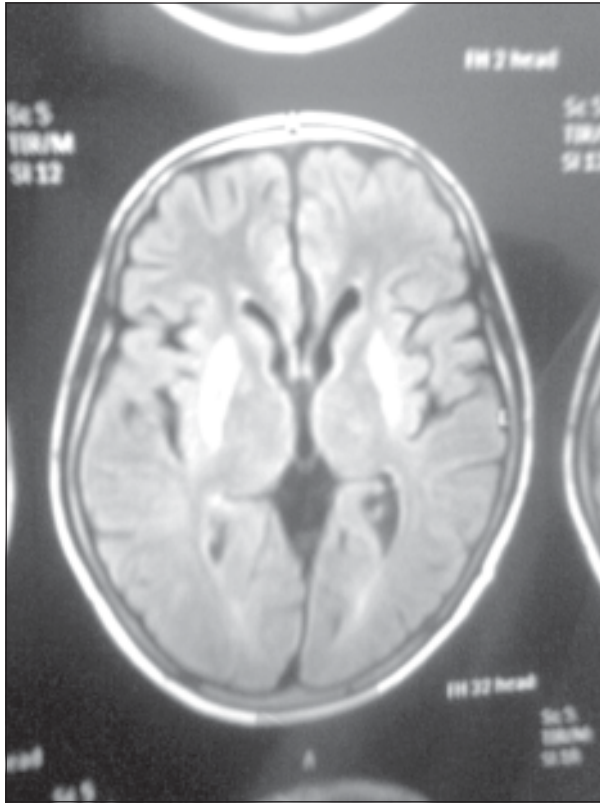


Fig-2: MRI of brain T1 with flare image showed bilateral basal ganglia hyper intensity

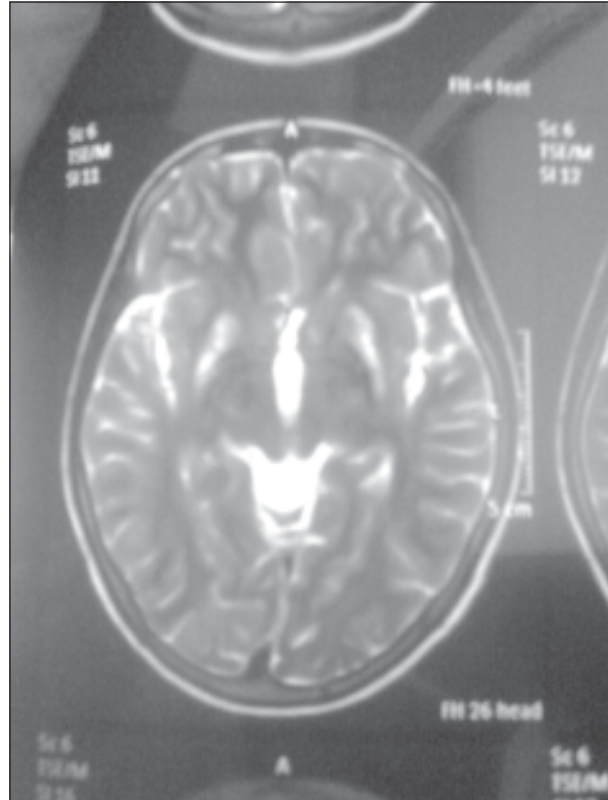


Fig-3: MRI of brain T-2 image showed hyper intense signal in bilateral basal ganglia .

although this is inadequate for either ruling in or ruling out Wilson's disease. The ceruloplasmin value is usually low in Wilson's disease, but in approximately 10% of patients it may be normal or near normal. The most useful screening procedure is a 24-h urine copper test.¹⁸⁻¹⁹ In symptomatic Wilson's disease 24-h urine copper is always elevated to a value greater than 100 µg per 24 h (normal is 50 or less). Another common screening procedure is a slit lamp examination for KF rings. Visual inspection is not adequate. KF rings are invariably present in the psychiatric and neurologic presentations; however, they are present in only about 50% of patients who present with liver disease. In a patient with classical clinical disease, KF rings, and elevated urine copper, the diagnosis can be made with certainty. If any question remains, the gold standard for diagnosis is a measure of quantitative copper in a percutaneous liver biopsy. Penicillamine challenge test is used to diagnosed a case of wilsons disease, Central nervous system imaging can be helpful in the diagnosis.

Family Screening:

First-degree relatives of any patient newly diagnosed with WD must be screened for WD (Fig.-3). Assessment should include: brief history relating to jaundice, liver disease, and subtle features of neurological involvement; physical examination; serum copper, ceruloplasmin, liver function tests including aminotransferases, albumin, and conjugated and unconjugated bilirubin; slit-lamp examination of the eyes for Kayser-Fleischer rings; and basal 24-hour urinary copper. Individuals without Kayser-Fleischer rings who have subnormal ceruloplasmin and abnormal liver tests undergo liver biopsy to confirm the diagnosis. Molecular testing for *ATP7B* mutations or haplotype studies should be obtained and may be used as primary screening.

Newborn Screening:

Measurement of ceruloplasmin in Guthrie dried-blood spots or urine samples from newborns may promote detection of individuals affected with WD, but further refinement of methodology involving immunologic measurement of ceruloplasmin is required before wide-scale implementation can be advised.⁴⁶⁻⁴⁸

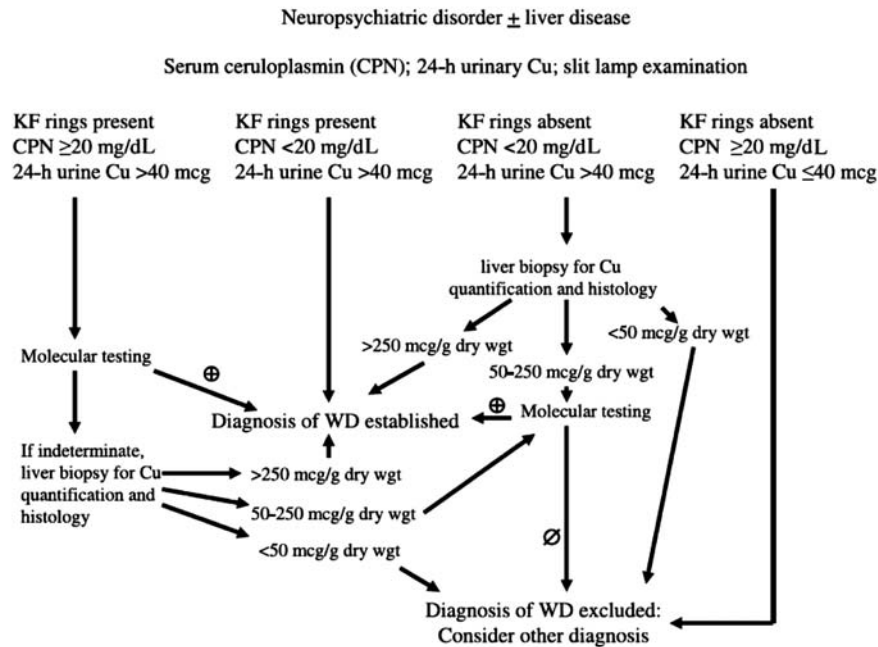


Fig-4: Diagnostic algorithm for Wilson's disease

Treatment

Wilson's disease is a condition that can be effectively treated by drugs. Treatment can be divided into initial therapy, maintenance therapy, and treatment of the presymptomatic patient and management of neurologic problem like tremor, chorea, dystonia, etc.^{19,20} Available pharmacologic agents include BAL, penicillamine, trientine, zinc acetate, and tetrathiomolybdate.

The aim of treatment is to reduce the amount of toxic free copper and reduce the complications of disease and drugs. Free copper is toxic whereas copper bound to ceruloplasmin or metallothionein is not. Although penicillamine demonstrated clear therapeutic advantages over BAL, initial neurologic worsening following initiation of penicillamine therapy is a concern.

Penicillamine:

Penicillamine has been available longer than the other anticopper drugs, and is therefore best known to physicians. However, it has serious short-comings of toxicity and neurologic worsening⁴⁷, and is being replaced by other equally effective, and less toxic, drugs. Penicillamine is a reductive chelator, and acts to mobilize copper from hepatic and other stores, and cause its excretion in the urine. The usual dose is 1.0 g/day, given as 500 mg twice daily (20 mg/kg/day in

2 div). Each dose should be given at least half an hour before meals or at least 2 h after meals. It is not uncommon in a newly treated patient to see urinary excretion of 5–10 mg of copper/day (normal is 20–50 mg/day, in untreated Wilson's it typically ranges from 100 to 1000 mg/day). Pyridoxine in a dose of 25 mg/day must be taken by patients on penicillamine therapy to avoid pyridoxine deficiency.

The side effects of penicillamine are numerous and often serious⁴⁷. There is an initial hypersensitivity involving 20–25% of patients. Other acute and subacute side effects include bone marrow suppression and proteinuria. Longer term side effects include autoimmune diseases such as systemic lupus erythematosus and Goodpasture's syndrome, effects on immune suppression leading to risk of infection. Risk for neurologic worsening was about 50% when penicillamine was used as initial treatment of neurologic Wilson's disease and that 50% of those who deteriorated never recovered to their pre penicillamine baseline.⁴¹ The majority of patients observed to have deteriorated did so within 4 weeks of beginning penicillamine therapy. It has been suggested that mobilization of large hepatic copper stores raises blood free-copper levels leading to increased toxic copper exposure to the brain and subsequent worsening.⁴¹ Thus, penicillamine should

never be given as initial treatment to patients with neurologic symptoms, since safer treatment alternatives (Table-III).

In a description of their experience Walshe and colleagues described outcomes following treatment of neurologic Wilson's disease with penicillamine. In this study if toxicity developed while using penicillamine, therapy was switched to trientine. In some patients in this series, trientine was used as first-line therapy, and in a small number zinc, BAL, or tetrathiomolybdate was used following penicillamine.

Because of concern for neurologic worsening in those treated with penicillamine, use of other agents has been recommended for initial treatment of neurologic Wilson's disease.^{14,20,24,42} If penicillamine is used, the standard starting dose is 250 mg four times a day or 500 mg twice a day. It has been suggested that starting with lower doses, 250–500 mg per day for a few weeks may lessen side effects.²⁶ When initiated, the patient should be carefully monitored for toxicities including to the bone marrow and kidney.

Trientine:

Trientine has considered to be safer alternative to penicillamine⁵⁰. It can cause neurologic worsening in approximately 25%.^{20,26} Trientine is a less potent copper chelator than penicillamine and promotes urinary excretion of copper⁵⁰. Trientine is used in doses of 750–1500 mg for initial therapy and 750 mg to 1000 mg for maintenance therapy, divided into two or three doses per day. It should be given 1 h before or 2 h after meals. Trientine shares some of the same side effects as penicillamine but at a much lower frequency. The most common perhaps, is proteinuria, occurring in 2-5% of patients. The risk of neurologic worsening in neurologically presenting patients, when trientine is used as initial therapy, is less than with penicillamine, a little lower than 20%. In a double-blind study comparing trientine to tetrathiomolybdate, 24% of those treated with trientine experienced neurologic worsening and in those who initially worsened 50% died.²⁰ While on trientine, urine copper is a reflection of enhanced urinary copper excretion and total body copper load. Upon initial treatment with trientine, 24-h urinary copper excretion may be 1000–3000 g (normal is 20–50 g/24 h). After a few weeks urinary copper decreases to 500–1000g per 24 h, and after approximately 1 year of therapy it should decrease to 200–500 g per 24 h. During the maintenance phase of trientine therapy keeping free copper below 25mg is the goal.

Zinc:

Zinc is fully effective in Wilson's disease as long as the patient complies with therapy Zinc acetate therapy has been used successfully as a preventive therapy in presymptomatic patients, as initial treatment for neurologic Wilson's disease, and as maintenance therapy following an initial course of decoppering.^{42,43} Zinc induces intestinal cell metallothionein, a protein that complexes intestinal food copper or endogenously secreted copper in saliva and gastric secretions. The complex cannot be absorbed in to the blood, and as intestinal cells die they, along with the complex, are sloughed into the stool resulting in a negative copper balance. The net effect of zinc therapy is an intestinal blockade of zinc absorption. Zinc has the additional effect of inducing hepatocyte metallothionein production, which may reduce the toxic effect of free copper in these cells.^{22,43} The decoppering effect of zinc is slow and a period of 4–8 months of treatment is required to reduce copper to nontoxic levels .

The dose of the zinc given below (table-II) and each of the dose separated from food & beverages other than water by at least 1h. The monitoring system for compliance and copper status with zinc therapy is superior to those with penicillamine and trientine therapy. That is because the urinary excretion of copper with zinc therapy is solely related to the body loading of “ freely available “ copper, and has nothing to do with the direct therapeutic action of the drug. Thus, during maintenance therapy, a target of 50-125 microgm/day urine copper should be sought & any progressive elevation above that level a cause for concern that the zinc is not being taken as prescribed. To avoid potential toxicities of trientine and penicillamine, some have successfully used zinc in the initial treatment of neurologic Wilson's disease.^{15,43,44} An advantage of zinc is its lack of serious significant side effects and safety in long-term use.⁴⁵ Approximately 10% experience gastric discomfort or nausea upon initiation of zinc therapy. Generally, gastric symptoms subside within days to weeks Table-II⁵⁴

Table-II

Dose adjustments for zinc in the pediatric patient

Age of weight	Dose
Until age 6 years	25 mg twice daily
6-15 years, or 125 pounds	25 mg three times daily
16 years or older, or 125 pounds or more	50 mg three times daily

Tetrathiomolybdate (TM)

TM has been used in Wilson's disease for the initial treatment of the neurologically presenting patient^{50, 53}. The dose is 120 mg/day, 20 mg three times/day with meals, and 60 mg at bedtime away from food, given for eight weeks, concomitant with zinc therapy. The measure of efficacy has been the rate of neurological deterioration, which has been less than 5% with TM.⁵³

TM acts by forming a tripartite complex with copper and protein. Given with food, TM binds with food copper and endogenously secreted copper, preventing copper absorption. Given between meals, TM is absorbed into the blood and forms a complex with free copper and albumin. Free copper in the blood is in equilibrium with tissue copper so that binding of serum copper to TM shifts the equilibrium to mobilize copper from tissue stores into serum where it is bound by TM and excreted into bile. The result is a rapid removal of tissue copper, which is then bound in the serum by TM, reducing potential copper toxicity, and significantly less neurologic worsening compared to penicillamine or trientine.^{17–20}

TM has a good safety profile.^{48,53} There is a 10–15% incidence of over treatment, anemia/leukopenia, responsive to lowering the dose. There is also a 10–15% incidence of a mild further increase in transaminase enzymes, probably due to TM's ability to shift copper out of hepatic metallothionein pools.

In a double-blind study 48 patients were randomized to TM or trientine for the initial treatment of neurologic Wilson's disease. Both trientine and TM were found to improve neurologic and speech function, but TM was significantly less likely to be associated with neurologic worsening than trientine. In the trientine arm 6 of 23 (26%) patients worsened neurologically, and 3 of those who worsened died. In the TM arm 1 of 25 (4%) patients developed neurologic deterioration, a statistically significant difference.

Dimercaprol:

Dimercaprol (INN) or **British anti-Lewisite** (abbreviated **BAL**), is a compound developed by British biochemists at Oxford University during World War II. Dimercaprol belongs to category of sulfhydryl compounds drugs. Dimercaprol is a type of heavy metal antagonist.

It binds to metals which produce toxicity by interacting with sulfhydryl containing enzymes in the body. The

dimercaprol metal complex spontaneously dissociates at a slow rate also dimercaprol is partly oxidised in the body; further emphasizing the necessity to have excess dimercaprol available in the body. But large amounts should not be given at a time. Dimercaprol once used as a drug therapy in Wilson's disease now not so. It acts as a Cu chelating agents in Wilson's disease. It is used as monotherapy or as an adjuvant to penicillamine in Cu poisoning and in Wilson's disease. Doses of dimercaprol in Wilson's disease is 300 mg (3 amp) daily for 10 days every 2nd month for long periods. It is very much painful in intramuscular injection. Many common side effect are rise in BP, tachycardia, vomiting, tingling and burning sensation, inflammation of mucous membranes, sweating, cramps, headache & anxiety.

Initial therapy of Neurologic Wilson's patients:

Recommended drug choices for patient presenting with the neurologic or psychiatric form of the disease are given in Table-III. A major problem exists with the initial therapy of neurologic patients in that all of the drugs currently available commercially have defects in treating these patients. Penicillamine has a high rate (estimated at about 50%) of causing neurologic worsening⁴⁶, probably by mobilizing hepatic copper and temporarily further elevating brain copper. About half of the patients who worsen never recover to their pre penicillamine baseline. Trientine, which is a chelator like penicillamine, appears to have about a 20% risk of causing neurologic worsening in these patients⁴⁸. We believe zinc is too slow acting to be optimal for these patients, and the disease may progress during the 4–6 months zinc requires to gain control of neurologic copper toxicity. Indeed, one of three patients who are treated with zinc alone had serious progression of tremor.

Because of the lack of a good drug for this type of patient recently new drug has developed tetrathiomolybdate (TM) for treating patients presenting with neurologic disease. In an open label study, only 2 of 55 patients reached quantitative neurologic function scoring criteria for neurologic worsening during initial treatment⁵³. These deteriorations may be the result of the natural history of the disease, whereas penicillamine and trientine deteriorations may be primarily drug catalyzed effects. This low rate of deterioration with TM was confirmed in a double blind study in which only 1 of 27 patients on TM reach criteria for deterioration, while 5 of 27 on trientine

reached criteria⁴⁸. The main disadvantage of TM is that it is not yet available commercially. TM has shown two side effects, an anemia/leukopenia, which we believe is due to over treatment and bone marrow copper depletion, and a mild further elevation of transaminase enzymes, which is probably due to TM shifting pools of copper in the liver^{48,53}. Both of these are responsive to dose reduction.

Given this background, it is recommended TM plus zinc as first choice (Table-IV). If this choice is unavailable, zinc therapy alone is recommended as safer than the 20% risk of deterioration with trientine, which is the third choice. Penicillamine should never be given to patients presenting with neurologic symptoms.⁵⁴

Maintenance therapy :

After elimination of acute copper toxicity by initial therapy maintenance therapy begins. Maintenance therapy can also be initiated from the beginning in asymptomatic patients and patients with only elevations of transaminase enzymes). After adequate treatment with a chelator, stable patients may be continued on a lower dosage of the chelating agent as maintenance therapy. Zinc or trientine are recommended. Penicillamine is not recommended because of its much greater toxicity. Zinc is preferred over trientine because of its lesser toxicity. Surrogate measures of this point include normal serum aminotransferase levels and hepatic synthetic function, non-ceruloplasmin bound copper concentration in the normal range (<25mg/dl), and 24-hour urinary copper repeatedly in the range of 200-500_g/day (3-8_mol/day) on treatment. The advantages of long-term treatment with zinc include that it is more selective for removing copper than trientine and penicillamine and few side effects

Recommended drug choices for maintenance therapy⁵⁴ are given in Table-III.

A. Anticopper drug choices initial therapy of neurologic/psychiatric patients

1st Choice	2nd Choice	3rd Choice
Tetrathiomolybdate	Zinc alone	Trientine and Zinc and Zinc

B. Anticopper drug choices for maintenance therapy and therapy of the presymptomatic patient

1st Choice	2nd Choice
Zinc	Trientine

A major problem with maintenance therapy is poor compliance⁴⁹. Because this is lifelong therapy, often involving young people, compliance tends to decrease over time. Thus, it can be expected that compliance problems in normal clinical practice will be even greater. An annual 24 h urine copper and zinc check, if on zinc, or an annual non-ceruloplasmin plasma copper determination if the patient is on trientine, are critically important parts of follow up to maximize compliance.

Therapy of the presymptomatic patient :

Presymptomatic patients are those that are diagnosed before becoming clinically ill. Usually these will be siblings of an affected patient who are diagnosed as a result of family screening. Occasionally presymptomatic patient will be identified when routine ophthalmologic exam reveals KF ring or when routine serum biochemistries reveal elevated serum transaminase enzymes. Presymptomatic patient are usually treated by zinc or trientine .

Symtomatic treatment:

Symtomatic treatment for dystonia and parkinsonian features and psychiatric disturbances can be very successfully reassuring for the patient of WD. The treatment of dystonia and parkinsonian features includes the administration o anticholinergics, tizanidine levodopa, baclofen, aminobutyric acid agonist- particularly clonazepam. 47 Botulinum toxin is a useful adjunct therapy in cases with severe limb dystonias when other treatments are unsuccessful. Convulsions can be controlled with traditional antiepileptic drugs. Psychiatric disturbance is usually managed with atypical neuroleptics

Prevention

Identification and treatment of presymptomatic Wilson’s disease patients can prevent development of symptoms. Aggressive screening measures of populations at risk are critical. An important target population is the siblings of the newly diagnosed patient. Each sibling has a 25% risk of being in the presymptomatic disease stage. Because prophylactic therapy will prevent the onset of the disease, these patients should be examined and disease status determined. All full siblings should be screened for blood ceruloplasmin, and 24-h urine copper levels. A 24-h urine copper in presymptomatic siblings with a value of 100 is diagnostic of Wilson’s disease.

Conclusion

The history of Wilson's disease is remarkable in many aspects. Unlike other neurodegenerative diseases this work has led to treatment that can essentially cure the disease. Unfortunately, neurologic Wilson's disease continues to suffer from clinically significant diagnostic delay. Currently available therapies have had a major positive impact on the outcome of neurologic Wilson's disease.

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