

Wilson's Disease

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ABSTRACT

Wilson's disease is an autosomal-recessive disorder caused by mutation in the *ATP7B* gene, with resultant impairment of biliary excretion of copper. Subsequent copper accumulation, first in the liver but ultimately in the brain and other tissues, produces protean clinical manifestations that may include hepatic, neurological, psychiatric, ophthalmological, and other derangements. Genetic testing is impractical because of the multitude of mutations that have been identified, so accurate diagnosis relies on judicious use of a battery of laboratory and other diagnostic tests. Lifelong palliative treatment with a growing stable of medications, or with liver transplantation if needed, can successfully ameliorate or prevent the progressive deterioration and eventual death that would otherwise inevitably ensue. This article discusses the epidemiology, genetics, pathophysiology, clinical features, diagnostic testing, and treatment of Wilson's disease.

KEYWORDS: Ceruloplasmin, copper, Wilson's disease, penicillamine, zinc

Although he was not the first to recognize the disease process,¹ in a doctoral thesis of more than 200 pages published in *Brain* in 1912, S. A. Kinnier Wilson masterfully provided the first detailed, coherent description of both the clinical and pathological details of the entity that now bears his name.² Many other individuals have embellished and expanded our understanding of Wilson's disease. Kayser in 1902³ and Fleischer in 1903⁴ and 1912⁵ described the rings of corneal pigmentation that are characteristic of Wilson's disease. Although Rumpel in 1913 first described increased hepatic copper content in Wilson's disease,⁶ it was not until the work of Mandelbrote et al⁷ and Cumings⁸ in 1948 that the disturbance of copper metabolism in Wilson's disease became clearly recognized. Ceruloplasmin deficiency in Wilson's disease was documented independently by Scheinberg and Gitlin⁹ and by Bearn and Kunkel¹⁰ in 1952, and the presence of impaired biliary excretion of copper by Frommer in 1974.¹¹ Recent years have brought dramatic advances in both the characterization of the genetic basis for Wilson's disease and in treatment capability.

EPIDEMIOLOGY

Wilson's disease is a rare autosomal-recessive disorder. A prevalence rate of 30 cases per million (or one per 30,000) and a birth incidence rate of one per 30,000 to 40,000 are often quoted.¹²⁻¹⁵ It has been estimated that there are ~600 cases of Wilson's disease in the United States and that ~1% of the population are carriers.¹⁴

GENETICS

A mutation in the *ATP7B* gene, located on chromosome 13, is responsible for Wilson's disease.¹⁶⁻¹⁹ The number of specific mutations that have been identified is now approaching 300.²⁰ Although missense mutations are most frequent, deletions, insertions, nonsense, and splice site mutations all occur.²¹ Most affected individuals are actually compound heterozygotes, having inherited different mutations from each parent. The large number of mutations has made commercial genetic testing for Wilson's disease impractical.

Whether the profusion of mutations accounts for the prominent variability in clinical presentation and age

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of symptom onset in Wilson's disease patients is unclear. The H1069Q mutation, which is the most frequent mutation in the United States and northern Europe, has been reported to be associated with later onset of symptoms and less severe disruption of copper metabolism,²² although not all studies support this assertion.²³ In contrast, nonsense and frameshift mutations may correlate with earlier onset of symptoms and more severe disturbance of copper metabolism.²⁴ Individuals with the same mutation, even homozygotic twins,²⁵ may demonstrate wide variability in age of symptom onset and clinical presentation, which suggests that additional factors are also operative. For example, recent reports propose that methionine homozygosity at codon 129 of the prion-related protein gene may influence the onset of symptoms in Wilson's disease.^{26,27}

It has been generally assumed that Wilson's disease carriers who possess a mutation in only a single allele do not develop symptoms of Wilson's disease. However, the development of depression and parkinsonism, recently described in three elderly sisters who were found to be heterozygotes for a nucleotide deletion at the 5'UTR region of the *ATP7B* gene,²⁸ calls this assumption into question.

PATHOPHYSIOLOGY

Copper is an essential element for cellular function, yet free copper is extremely toxic and can produce irreversible cellular damage. To cope with this, elegant systems have evolved that bind the copper molecule to ensure safe transport of necessary copper to intended sites and safe elimination of excess copper through the biliary system. Both the *ATP7B* protein and ceruloplasmin are involved with copper transport.

The *ATP7B* protein normally resides in the trans-Golgi network in hepatocytes, where it mediates the incorporation of six copper molecules into apoceruloplasmin, forming ceruloplasmin.²⁹ Under high copper conditions, however, *ATP7B* is also redistributed to cytoplasmic vesicles where it transports excess copper across the hepatocyte apical membrane into the bile canaliculus for subsequent biliary excretion.^{30,31} In individuals with Wilson's disease, mutation in the *ATP7B* gene results in defective *ATP7B* protein that cannot perform these functions. Consequently, copper progressively accumulates within the hepatocytes. Not only does this progressive copper accumulation ultimately compromise hepatic function, the hepatic storage capacity is also eventually exceeded and unbound copper spills out of the liver and is deposited in other organs and tissues, where it also provokes damage and dysfunction. As the excess copper escapes from the liver, urinary copper excretion rises dramatically, but is unable to compensate fully for the defect in biliary excretion. It has been assumed that the cellular damage

characteristic of Wilson's disease is due to a direct toxic effect of excess copper. Recent evidence, however, suggests that a reduction in the protein, X-linked inhibitor of apoptosis (XIAP), induced by copper elevation, results in acceleration of caspase 3-initiated apoptosis with resultant cell death.³²

Because of the defect in *ATP7B*-mediated incorporation of copper into apoceruloplasmin, ceruloplasmin deficiency is also characteristic of Wilson's disease. However, this deficiency is neither universally present nor absolutely diagnostic of Wilson's disease. As many as 5 to 15% of individuals with Wilson's disease may have normal or slightly reduced ceruloplasmin, whereas 10 to 20% of heterozygotes who are clinically asymptomatic have reduced ceruloplasmin.^{13,14,33}

CLINICAL FEATURES

Although the fundamental pathogenetic defect of Wilson's disease lies within the hepatobiliary system, the consequences of the relentless copper accumulation are played out on a multisystemic battlefield. The damage that rampaging copper can inflict on various organs and tissues produces a clinical picture of striking diversity that, in turn, can present a daunting diagnostic challenge.

Hepatic Manifestations

In ~40 to 50% of individuals with Wilson's disease, hepatic dysfunction is the initial clinical manifestation.^{14,34} The average age of onset for those who present with hepatic symptoms is 11.4 years.³⁵ It is rare for symptoms to begin before age 5 years, although Wilson's disease has been diagnosed as early as 2 years of age in a child presenting with persistent elevation of liver enzymes.³⁶ Hepatic presentation beyond age 40 years is also unusual; however, in a report from one center, 17% of patients were older than 40 years at the time of diagnosis.³⁷

Hepatic dysfunction in Wilson's disease may assume several forms. Asymptomatic enlargement of the liver and spleen may occur, sometimes with elevation of liver enzymes. Acute transient hepatitis is the mode of presentation in 25% of those in whom hepatic symptoms herald disease onset. Although this may be mistaken for viral hepatitis by the unwary, the presence of hemolytic anemia in conjunction with the hepatic dysfunction, or elevation of unconjugated (indirect) bilirubin, should alert the clinician to the possibility of Wilson's disease.¹⁴ The hepatic symptoms of Wilson's disease may also mimic autoimmune hepatitis^{38,39}; it is in this setting that ceruloplasmin, as an acute-phase reactant, may rise transiently into the low normal range.^{14,39} Wilson's disease can also make its appearance as acute fulminant hepatitis. Indeed, ~5% of all cases of acute liver failure

are due to Wilson's disease.⁴⁰ The mortality rate with this mode of presentation is alarmingly high; individuals typically are younger than 30 years and two-thirds are female.⁴¹ A severe Coombs-negative hemolytic anemia, presumably due to intravascular hemolysis triggered by the sudden release of massive amounts of copper into the bloodstream from the failing liver, is often present.⁴² The most frequent mode of hepatic presentation of Wilson's disease, however, is the development of progressive cirrhosis. The cirrhosis has no Wilson's disease-specific features. Because of the varied modes of hepatic presentation that Wilson's disease can assume, any individual younger than age 50 years with unexplained liver disease should be screened for Wilson's disease.¹⁴

Neurological Manifestations

Neurological dysfunction constitutes the initial clinical manifestation in 40–60% of individuals with Wilson's disease.^{14,34} The average age of symptom onset in persons who present with neurological dysfunction is 18.9 years, although neurological symptoms may appear as early as age 6 years.⁴³ On the other end of the age spectrum, onset of neurological symptoms as late as age 72 years has been described.⁴⁴

Tremor, which may be resting, postural, or kinetic, is the most frequent initial neurological feature of Wilson's disease. Proximal upper extremity tremor may take on a coarse, "wing-beating" appearance, but Wilson's disease tremor may also be distal and quite small in amplitude. Head titubation may also appear. The many guises that Wilson's disease tremor may assume make it important to consider and exclude the possibility of Wilson's disease in any individual, but especially young persons, with tremor.

Dysarthria is also common in persons with Wilson's disease and may possess either an extrapyramidal or a cerebellar character.⁴⁵ Dystonia involving the tongue, face, and pharynx may produce not only dysarthria, but also drooling and an unusual perturbation of facial expression that results in a frozen grimace (*risus sardonicus*). A peculiar "whispering dysphonia" has been described in Wilson's disease,⁴⁶ as has a laugh in which most of the sound is generated during inspiration.⁴⁷

A variety of other neurological features may emerge in Wilson's disease. Cerebellar dysfunction develops in ~25% of individuals with neurological Wilson's disease.⁴⁸ Dystonia may be present in almost 40%.⁴⁹ Gait abnormalities are a frequent component of neurological Wilson's disease; both extrapyramidal and cerebellar patterns may develop. Chorea, tics, and myoclonus are unusual, although severe generalized myoclonus associated with extensive white matter lesions has recently been described.⁵⁰ The painless variant of painful legs and moving toes syndrome has also been reported in a person with Wilson's disease.⁵¹ Although not often

mentioned in reviews of Wilson's disease, autonomic dysfunction is noted by some investigators to be present in 26 to 30% of persons with the disease.^{52,53}

Seizures are an infrequent component of Wilson's disease, but may occur in up to 6% of patients.⁵⁴ Partial seizures occur most frequently, and benign epilepsy of childhood with centrotemporal spikes has been observed.⁵⁵ Status epilepticus is rare, but does occur.⁵⁶ Headache or seizure may occur in the setting of Wilson's disease and may be the initial neurological symptom in approximately 10% of patients.¹³ Neither upper motor neuron nor lower motor neuron dysfunction is typically present in Wilson's disease. However, peripheral sensorimotor polyneuropathy with both demyelinating and axonal involvement has been reported as the initial manifestation of Wilson's disease.⁵⁷ Olfactory impairment has recently been reported in persons with Wilson's disease who have neurological dysfunction.⁵⁸ The severity of the olfactory deficit parallels the severity of neurological dysfunction. Pseudobulbar emotional lability, hypersomnia, altered rapid eye movement (REM) sleep function, priapism, and muscle cramps have all also been noted in individuals with Wilson's disease.

Psychiatric Manifestations

The frequency with which Wilson's disease makes its clinical appearance in the form of psychiatric dysfunction is unsettled. Although most reports indicate a frequency in the range of 20%, some investigators have noted that psychiatric features were evident at the time of initial presentation in 65% of individuals with Wilson's disease, and that these symptoms had been sufficiently severe to warrant psychiatric intervention in almost 50% before the diagnosis of Wilson's disease was made.⁵⁹ Psychiatric symptoms appear at some point in time in most individuals with Wilson's disease, and most frequently in persons who also display neurological dysfunction, reflecting the central nervous system (CNS) origin of both.

A variety of psychiatric symptoms may appear in the setting of Wilson's disease. Personality changes and disturbances of mood, particularly depression, are the most frequent behavioral features of Wilson's disease.⁶⁰ Depression may be severe, and in one study almost 16% of patients had a history of suicide attempts.⁶¹ Psychosis is unusual in Wilson's disease, but may occur.⁶² Antisocial or criminal behavior has been reported in Wilson's disease,⁶³ as has sexual preoccupation and disinhibition.^{13,59}

Cognitive impairment may develop in Wilson's disease, but is often more apparent than real.⁶⁰ Nevertheless, cognitive difficulties including impairment of frontal-executive ability, visuospatial processing, and some aspects of memory have been reported.⁶⁴ A range of abnormalities on formal neuropsychological testing has also been described.⁶⁵

Because of the varied and sometimes subtle way in which the psychiatric features of Wilson's disease can present, Wilson's disease should be considered and excluded in any young person who develops unexplained psychiatric dysfunction, especially when any signs of neurological dysfunction are also present. Poor school performance, especially if coupled with abdominal symptoms, should prompt consideration of Wilson's disease.⁶⁶ The possibility of Wilson's disease should also be considered in young persons suspected of drug abuse, because the symptoms can be similar.^{14,67}

Ophthalmological Manifestations

The description by Kayser³ and Fleischer⁴ of pigmented corneal rings antedated Wilson's description of Wilson's disease² by about a decade, with Fleischer subsequently making the connection between the two in his 1912 publication.⁵ Kayser-Fleischer rings are formed by deposition of copper within Descemet's membrane. Excess copper is actually deposited throughout the cornea in Wilson's disease, but it is only in Descemet's membrane that sulfur-copper complexes are formed, producing the visible copper deposits.^{68,69} Kayser-Fleischer rings are almost always bilateral, but unilateral formation has been reported.⁷⁰ The color of the rings can range from gold to brown to green; consequently, they can be difficult to see in individuals with brown irises. Ring formation first becomes visible in the superior aspect of the cornea, followed by the inferior aspect, with subsequent filling in of the medial and lateral aspects. It is important, therefore, to lift the eyelid and expose the entire cornea when looking for Kayser-Fleischer rings.⁷¹ The pigment first appears in the corneal periphery at the limbus, with subsequent spread centrally.

Kayser-Fleischer rings are virtually always present in persons with Wilson's disease who have developed neurological or psychiatric dysfunction, although case reports documenting the absence of Kayser-Fleischer rings in Wilson's disease patients with neurological symptoms exist.⁷² Kayser-Fleischer rings may not have yet formed in presymptomatic individuals or those with only hepatic involvement. Because it is sometimes difficult to visualize Kayser-Fleischer rings during routine ophthalmological examination, it is very important to include slit lamp examination by a neuro-ophthalmologist or an ophthalmologist experienced in the diagnostic evaluation of individuals in whom Wilson's disease is suspected. Complicating matters further, corneal deposition of copper can occur in several other situations, and occasionally corneal staining that is unrelated to copper can imitate Kayser-Fleischer rings.⁷³

The other classic ophthalmological manifestation of Wilson's disease is the sunflower cataract, which was first described by Siemerling and Oloff in 1922.⁷⁴ Sunflower cataracts are relatively rare in Wilson's disease

patients, occurring in only 17% in one study.⁶⁸ They consist of copper deposition in the lens that assumes a sunburst or sunflower appearance, with a central disc and radiating petal-like spokes.^{68,75}

Other Manifestations

Bone and joint involvement are under-recognized components of Wilson's disease. Radiographic evidence of osteoporosis is present in up to 88% of persons with Wilson's disease.^{76,77} Spontaneous fractures may result. Joint involvement, especially at the knees, is also common and joint pain may be the presenting symptom of Wilson's disease.⁷⁷ Radiological evidence of vertebral column abnormalities is evident in 20 to 33% of individuals with Wilson's disease.^{76,78}

Hemolytic anemia, presumably due to copper-induced oxidative damage to erythrocytes, may be the initial manifestation of Wilson's disease in 10 to 15% of cases.⁷⁹⁻⁸¹ In the setting of fulminant hepatic failure, the presence of concomitant hemolytic anemia may be an important diagnostic clue for Wilson's disease.¹⁴ Thrombocytopenia may also develop, either in conjunction with hemolytic anemia or separately.⁸² A recent report describes a patient with thrombocytopenia and the combination of Wilson's disease and antiphospholipid antibody syndrome.⁸³

Renal involvement may also occur in Wilson's disease. Renal tubular dysfunction, with consequent hypercalciuria and hyperphosphaturia, may induce nephrocalcinosis.⁸⁴ Hypokalemia with muscle weakness and even respiratory failure has also been reported in Wilson's disease, presumably secondary to renal tubular dysfunction.⁸⁵

Skin changes with hyperpigmentation of the anterior lower legs, potentially misinterpreted as Addison's disease, may develop in Wilson's disease.⁸⁶ Gynecological abnormalities (menstrual irregularity, delayed puberty, gynecomastia),^{87,88} cardiovascular dysfunction (congestive heart failure, cardiac arrhythmia), and other impairments (glucose intolerance, parathyroid insufficiency) have also been described.⁷⁹

DIAGNOSTIC TESTING

Although genetic testing may provide definitive proof of the diagnosis of Wilson's disease, the multitude of documented mutations identified in Wilson's disease makes commercial genetic testing impractical. Advances and refinements in technology may make this possible in the future, but currently the diagnosis of Wilson's disease still must be made by the judicious employment of a combination of diagnostic tests. The specific tests necessary differ depending on whether the mode of clinical presentation implicates dissemination of copper beyond the confines of the liver.

Hepatic Copper Determination

Determination of hepatic copper content by means of liver biopsy is the single most sensitive and accurate available test for Wilson's disease. Hepatic copper content is elevated in the vast majority of individuals with Wilson's disease, even those who are clinically asymptomatic. Elevations greater than 250 $\mu\text{g/g}$ of dry tissue (normal = 15 to 55 $\mu\text{g/g}$) are typically present. However, in a recent study of 114 liver biopsies from individuals with Wilson's disease, hepatic copper content was greater than 250 $\mu\text{g/g}$ in only 83.3%, and was less than 50 $\mu\text{g/g}$ in 3.5%.⁸⁹ Hepatic copper elevation is not pathognomonic for Wilson's disease; it can also be present in liver diseases such as primary biliary cirrhosis, biliary atresia, extrahepatic biliary obstruction, primary sclerosing cholangitis, autoimmune (chronic active) hepatitis, and others.^{90,91} The invasiveness of liver biopsy and the small but real risk of complications from the procedure argue against its use in every individual suspected of Wilson's disease. It should be reserved for situations where simpler approaches have not yielded a definitive diagnosis. Liver biopsy is usually not necessary in individuals with neurological or psychiatric dysfunction because other tests permit diagnosis; its primary use is in individuals presenting with hepatic dysfunction, where copper may not yet have been discharged from the liver to flood other organs and tissues.

Slit-Lamp Examination

In an individual with neurological or psychiatric dysfunction, the presence of Kayser-Fleischer rings strongly supports a diagnosis of Wilson's disease. However, the absence of Kayser-Fleischer rings in individuals with CNS dysfunction has been reported.^{61,72,92} Kayser-Fleischer rings are often absent in patients with only hepatic symptoms. In one study of 36 children (ages 7 to 17 years) with Wilson's disease, Kayser-Fleischer rings were present in only two (5.6%) on slit-lamp examination.⁹³

Ceruloplasmin

Measurement of serum ceruloplasmin is safe, simple, and practical as a screening test for Wilson's disease, but it is not sufficient by itself. As mentioned earlier, ceruloplasmin may fall within or only slightly below the normal range in 5 to 15% of individuals with Wilson's disease, whereas 10 to 20% of heterozygotes may have reduced levels.^{13,14,33} Ceruloplasmin may also be abnormally low in other conditions (Menkes' disease, aceruloplasminemia, sprue, nephritic syndrome, protein-losing enteropathy) and in chronic liver disease of any cause.⁷³ In contrast, as an acute phase reactant, ceruloplasmin may become transiently elevated into the

normal range in Wilson's disease patients by infection or inflammation, or by birth control pills or steroid ingestion.³⁸

Measurement of 24-Hour Urinary Copper Excretion

The 24-hour urinary copper measurement may be the single best screening test for Wilson's disease, especially in individuals with neurological or psychiatric dysfunction.¹⁴ Urine copper levels in symptomatic Wilson's disease patients typically exceed 100 $\mu\text{g/d}$. Urine copper may, however, be elevated in some other conditions. Heterozygous Wilson's disease carriers may have modestly elevated urine copper levels, but not above 100 $\mu\text{g/d}$.¹⁴ Urine copper levels can also be elevated in obstructive liver disease. It is important that patients collect their urine in copper-free jugs supplied by the laboratory to prevent spurious elevations.

Serum Copper and Serum Free (Non-Ceruloplasmin Bound) Copper

Routine serum copper levels, which measure total (both bound and unbound) serum copper, are of little diagnostic value in Wilson's disease, even though they typically are reduced. Copper bound to ceruloplasmin normally represents $\sim 90\%$ of total serum copper.¹⁴ Therefore, the reduction in total serum copper in Wilson's disease simply is a reflection of reduced ceruloplasmin.^{14,79}

In contrast, determination of non-ceruloplasmin bound copper reflects the copper that is free to be deposited in tissue and, thus, is potentially toxic.⁷⁹ This copper fraction is typically elevated in Wilson's disease. It is often difficult to get laboratories to measure non-ceruloplasmin bound copper, but the level can be calculated by multiplying the number for the ceruloplasmin level (reported in mg/dL) by three and then subtracting that sum from the total serum copper level (reported in $\mu\text{g/dL}$).^{14,94} The normal range for non-ceruloplasmin bound copper is 10 to 15 $\mu\text{g/dL}$.

Neuroimaging Studies

Recent reports have demonstrated the presence of magnetic resonance imaging (MRI) abnormalities in virtually 100% of Wilson's disease patients with neurological dysfunction.⁹⁵ A multitude of MRI abnormalities has been described in Wilson's disease; the presence of increased signal intensity in the basal ganglia on T2-weighted images is perhaps the most widely recognized, although generalized brain atrophy may be more common.^{94,95} Abnormalities such as the "face of the giant panda" in the midbrain, the "face of the miniature panda" in the pons, and the "bright claustrum" sign are

present in only a relatively small percentage of individuals with Wilson's disease.^{94,95}

Positron emission tomography (PET) scanning shows abnormalities in Wilson's disease, but is not routinely available. Transcranial brain parenchyma sonography has been explored in the setting of Wilson's disease. Lenticular hyperechogenicity was present in 100% of 17 assessable Wilson's disease patients with neurological dysfunction and in two of three neurologically asymptomatic individuals.⁹⁶

Other Studies

Incorporation of radioactive copper into ceruloplasmin may be of value in select situations in the diagnostic evaluation of suspected Wilson's disease, but is seldom required. It has been suggested that cerebrospinal fluid (CSF) copper levels may provide the most accurate reflection of the brain's copper load,⁹⁷ but this test is also not routinely employed.

TREATMENT

With the exception of liver transplantation, treatment of Wilson's disease is only palliative and intended to restore and maintain copper balance. It does not eliminate the underlying defect responsible for Wilson's disease. Thus, a lifelong commitment to treatment is required. Limitation of dietary copper intake is generally ineffective, and pharmacological management is necessary.

Zinc

First proposed by Schouwink in his doctoral thesis in 1961, the use of zinc in the treatment of Wilson's disease has gradually assumed an increasingly important role in the management of the disease.⁹⁸ Administered either as acetate, sulfate, or gluconate, zinc reduces intestinal absorption of dietary copper via induction of metallothionein formation in intestinal enterocytes. The increased metallothionein then binds both zinc and copper, trapping them within the intestinal mucosal cells, which are eventually sloughed and excreted in the feces.

Zinc induction of metallothionein is a relatively slow process, and the negative copper balance produced is relatively small. Therefore, zinc has primarily been used as maintenance therapy following initial treatment with more potent "decoppering" agents.¹⁴ However, some investigators also advocate using zinc monotherapy as initial treatment for Wilson's disease and report consistent success.⁹⁸ The usual dosage regimen for zinc is 50 mg of elemental zinc three times daily (zinc sulfate tablets contain 220 mg of zinc sulfate salt, which translates to 50 mg of elemental zinc; zinc acetate is labeled by its elemental zinc content). Zinc is generally well tolerated, although gastric discomfort may occur.

Penicillamine

Penicillamine, a metabolic byproduct of penicillin that avidly chelates copper, was introduced as a treatment for Wilson's disease by Walshe in 1956⁹⁹ and quickly became the standard of therapy. Following initiation of treatment, copper is rapidly mobilized from tissues and eliminated in the urine. Functional improvement may become evident within 2 weeks of treatment initiation, although it typically takes somewhat longer. Improvement in virtually all facets of function may occur, although psychiatric symptoms improve less consistently than neurological symptoms.⁶⁰

The usual dosage of penicillamine for initial treatment is 250–500 mg four times daily, given on an empty stomach, although some advocate lower dosages. There is no consensus on the need for supplemental pyridoxine (penicillamine is a pyridoxine antagonist). In recent years, increasing attention has been directed toward the propensity of penicillamine to produce deterioration in neurological function on initiation of treatment.^{98,100} The frequency with which this occurs is a subject of some disagreement. Walshe and Yealland noted it in 22% of patients that they treated,¹⁰¹ whereas Brewer and colleagues described it in 53%; they further reported that 50% of those who experienced neurological deterioration on initiation of treatment never recovered to their baseline level of functioning.^{14,102} The reason for this deterioration is uncertain. Mobilization of copper from the liver with subsequent redistribution to the brain has been suggested,¹⁰² but studies of CSF copper levels during this deterioration do not support this hypothesis.⁹⁷ There is some evidence that this penicillamine-induced neurological deterioration may be less likely to occur if lower doses of penicillamine are used.¹⁰³

Penicillamine can also produce a variety of other adverse effects. Acute sensitivity reactions with skin rash, fever, eosinophilia, thrombocytopenia, leukopenia, and lymphadenopathy develop in 20 to 30% of patients and often necessitate abandonment of penicillamine treatment.^{104,105} Penicillamine dermatopathy, with brownish skin discoloration, is a consequence of recurrent subcutaneous bleeding during incidental trauma.¹⁰⁶ With chronic penicillamine administration, a host of other drug-induced complications may occur, including nephrotic syndrome, Goodpasture's syndrome, a lupus-like syndrome, a myasthenia-like syndrome, acute polyarthritis, thrombocytopenia, retinal hemorrhages, and loss of sense of taste.⁷³

Trientine

Trientine is a copper chelating agent with a mechanism of action similar to penicillamine. As concerns have grown regarding the potential complications of penicillamine, more attention has been focused on trientine because it provokes a less precipitous decoppering and,

thus, may be safer to use. As with penicillamine, trientine should be taken on an empty stomach. The usual daily dose is 750 to 2000 mg, divided into three doses.

Experience with trientine is still less extensive than that with penicillamine, but in a recent study the risk of neurological deterioration when trientine was used as the initial therapy for Wilson's disease was 26%.¹⁰⁰ Of those patients who experienced neurological deterioration, 83% either died or did not fully recover. Lupus nephritis and sideroblastic anemia have also been reported with trientine.

Tetrathiomolybdate

First tested as a potential treatment for Wilson's disease in 1984,¹⁰⁷ tetrathiomolybdate has been shepherded toward availability as a treatment for Wilson's disease, primarily by Brewer and colleagues.^{14,100} Although it currently remains an experimental agent and is unavailable for general use, it is included in this article because approval for commercial use may be near.¹⁰⁰

Tetrathiomolybdate has a distinct, dual mechanism of action in that it both limits gastrointestinal absorption of copper by forming a nonabsorbable tripartite complex with copper and albumin within the gut lumen, and also forms the same complex within the bloodstream, preventing cellular uptake of free copper.^{14,100} However, taking advantage of this dual capability requires a somewhat complicated dosing scheme. Tetrathiomolybdate binds copper in the gut when it is given with food and is absorbed into the bloodstream when it is given without food. Therefore, a 20-mg dose is given six times per day—three times daily with meals and three times daily between meals.^{20,100} Tetrathiomolybdate is not intended for long-term treatment, but only for an initial 8-week period, to be followed by long-term maintenance therapy with zinc.

In contrast to penicillamine and trientine, neurological deterioration occurs in only 4% of individuals treated with tetrathiomolybdate.^{14,100} The drug is generally tolerated well, although bone marrow depression with anemia or leukopenia may occur.^{14,100}

Liver Transplantation

In patients with Wilson's disease who develop fulminant hepatic failure, the mortality rate with medical treatment approaches 100%.^{41,108} Orthotopic liver transplantation has proved to be an effective treatment for this dreaded development. In a recent report summarizing the experience of a consortium of Italian centers, patient survival rates were 89.1% at 12 months, 82.9% at 3 years, 75.6% at 5 years, and 58.8% at 10 years.¹⁰⁹ Individuals with both neuropsychiatric and hepatic dysfunction had a lower mean survival rate than patients with hepatic dysfunction alone

(79 versus 135 months). Living-related donor transplantation has also been successfully employed in Wilson's disease,^{110,111} although copper metabolism may remain suboptimal if the donor was a Wilson's disease carrier.¹¹¹ The primary indication for orthotopic liver transplantation in Wilson's disease is hepatic failure; its use for treatment of progressive neurological deterioration is controversial.

DIAGNOSTIC AND TREATMENT GUIDELINES

In persons with Wilson's disease presenting with hepatic dysfunction, 24-hour urinary copper content is usually elevated and ceruloplasmin reduced. Kayser-Fleischer rings are not consistently present. Liver biopsy is generally used to confirm increased hepatic copper content and to document the degree of hepatic injury. In most individuals with neurological or psychiatric dysfunction, the presence of Kayser-Fleischer rings on slit-lamp examination, along with appropriately elevated 24-hour urinary copper and reduced ceruloplasmin levels, is sufficient to confirm diagnosis and makes liver biopsy unnecessary.

In individuals with Wilson's disease who are still asymptomatic, treatment can be initiated and maintained with zinc alone. Most investigators believe that individuals who have developed symptoms initially require more vigorous removal of copper, although the use of zinc monotherapy in this situation has strong advocates.⁹⁸ Either penicillamine or trientine can be used in these patients, but the danger of initial deterioration in neurological function hovers above both these treatment modalities, especially penicillamine. Should tetrathiomolybdate become commercially available, it may supplant both of these agents. Liver transplantation currently remains reserved for patients who have developed hepatic failure despite optimal medical management.

For individuals with Wilson's disease being managed medically, treatment is a lifelong necessity, and compliance must be zealously monitored. Compliance with zinc therapy can be assessed by measurement of 24-hour zinc and copper levels. A 24-hour urinary zinc level of less than 2 mg indicates inadequate compliance.¹⁴ Monitoring compliance with penicillamine or trientine therapy is a bit more difficult, but a spike in a previously receding or stable 24-hour urinary copper level may indicate noncompliance.¹⁴ Monitoring serum non-ceruloplasmin bound copper can also be used.

Prolonged treatment with both zinc and chelating agents can induce copper deficiency. Anemia may be the first sign of this.¹⁴ In patients on zinc maintenance therapy, a 24-hour urinary copper level below 35 μg is suggestive of copper deficiency due to overtreatment. For individuals on trientine or penicillamine, a serum

non-ceruloplasmin bound copper level below 5 μg suggests overtreatment.¹⁴

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