

SPECIAL REPORTS AND REVIEWS

Wilson Disease

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In the spring of 1912, Samuel Alexander Kinnier Wilson, a young registrar at the National Hospital, Queen's Square, London, described the detailed clinical and pathologic findings of 4 patients, all of whom, he believed, had the same disease. He also included careful descriptions of 8 similar patients from the literature, in each case pointing out the clinical features of progressive lenticular degeneration in association with the pathologic findings of hepatic cirrhosis.^{1,2} Although Wilson believed that hepatic involvement was not a significant factor in the evolution of the disease, the prominent role of hepatic cirrhosis in the clinical presentation was soon readily apparent.³ In 1948, Cummings⁴ showed the presence of excess copper in the tissues of affected individuals, and soon thereafter Scheinberg and Gitlin⁵ showed a deficiency of ceruloplasmin in the serum of patients with Wilson disease. A simple and effective treatment for many patients became available when Walshe⁶ introduced penicillamine as an oral copper chelator.

The recognition that Wilson disease is a disorder of copper homeostasis gave rise to the hypothesis that specific cellular mechanisms govern the metabolism of this metal and led to a pursuit to define the molecular basis of this disease. Detailed family studies indicated that Wilson disease is inherited as an autosomal recessive disorder, and linkage analysis with a multisibship inbred pedigree established that the affected gene was localized^{7,8} on chromosome 13. Subsequent identification of the Wilson disease gene showed that this locus encodes a copper-transporting P-type adenosine triphosphatase (ATPase) that is highly evolutionarily conserved and permits the efficient excretion of copper into the bile.⁹⁻¹¹ Elucidation of the molecular genetic basis of Wilson disease has provided fundamental insights into the mechanisms of cellular inorganic biochemistry and permitted the development of novel diagnostic and therapeutic approaches in a number of human diseases.¹²

Copper Metabolism

Physiology

Copper is an essential trace element that permits the facile transfer of electrons in a diverse, yet essential,

group of cuproenzymes required for cellular respiration, iron oxidation, pigment formation, neurotransmitter biosynthesis, antioxidant defense, peptide amidation, and connective tissue formation.¹² Numerous dietary foods are rich in copper that is absorbed primarily through the stomach and duodenum. Biliary excretion is the only physiological route for copper elimination, and each day an amount of copper is excreted in the bile that is equivalent to that absorbed.

The liver plays a critical role in copper metabolism, serving as the site of storage for this metal and the primary determinant regulating biliary excretion.¹³ Studies using copper isotopes show rapid clearance of this metal from the portal circulation, with 10% of the isotope reappearing in the serum bound to the plasma protein ceruloplasmin within 24 hours after a single dose.¹⁴ Ceruloplasmin is a ferroxidase that has an essential role in iron metabolism and contains greater than 95% of the plasma copper.¹⁵ The remaining copper present in the plasma is bound to amino acids, and it is believed that these complexes provide the mechanism for transport of this metal to various tissues. Renal filtration plays a role in copper excretion only under rare circumstances when tubular reabsorption is exceeded.

The uptake and storage of copper in the liver occurs in hepatocytes, and it is these cells that determine the rate of biliary excretion of this metal. The essential role of hepatocytes in copper metabolism is shown by the normalization of copper homeostasis in copper-overloaded individuals with Wilson disease after liver transplantation.¹⁶ At steady state, the amount of copper excreted in the bile is directly proportional to the size of the hepatic copper pool. The hepatocyte is capable of rapidly increasing biliary copper excretion in response to increases in systemic copper, and, therefore, hepatic copper overload is an unusual occurrence under physiological conditions.¹⁷ There is no enterohepatic circulation of copper, and once excreted into the bile, this metal exists as an unabsorbable complex that is excreted in the stool. Cer-

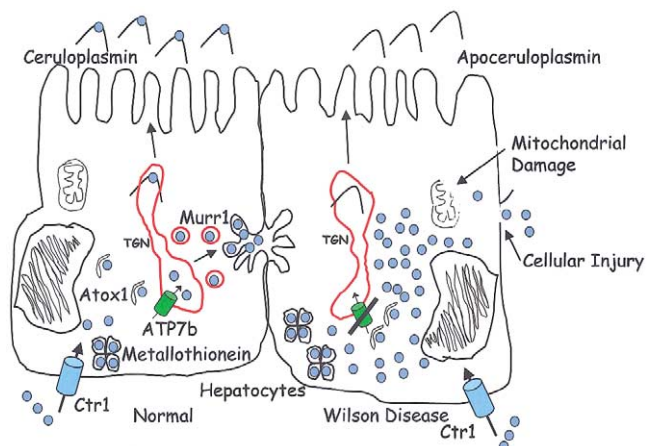


Figure 1. Illustration of the proteins and pathways critical for hepatocyte copper metabolism. The Wilson disease ATPase, ATP7b, transports copper into the trans-Golgi network (TGN) and late secretory pathway. In Wilson disease, inherited loss-of-function mutations in the gene encoding ATP7b result in cytosolic copper accumulation with associated cellular injury. Reprinted with permission from the American Association for the Study of Liver Diseases.¹³

uloplasmin is synthesized in hepatocytes and secreted into the plasma after the incorporation of copper late in the secretory pathway.¹⁵ Failure to incorporate copper during ceruloplasmin biosynthesis results in the secretion of an apoprotein that is devoid of enzymatic activity and rapidly degraded. For this reason, the serum ceruloplasmin concentration can be a useful indicator of copper status. In copper deficiency, as hepatic copper stores decrease, there is minimal copper available for transport into the hepatocyte secretory pathway, and the biliary copper content and serum ceruloplasmin concentration are diminished.¹⁸

The human fetus acquires copper by placental transport and subsequently stores this metal in the developing liver. The hepatic copper content at birth is increased relative to later in life because of a developmental decrease in biliary excretion in utero.¹⁹ As a consequence, copper is unavailable to the hepatocyte secretory pathway, and the newborn liver predominantly secretes apoceruloplasmin that is devoid of copper and is turned over rapidly in the serum. This developmental physiology abrogates the use of serum ceruloplasmin for newborn screening to identify asymptomatic individuals with Wilson disease. As bile flow increases after birth, copper is transported into the secretory pathway of the hepatocyte, with a resultant increase in the serum ceruloplasmin concentration and the biliary copper content.²⁰ Although ceruloplasmin contains almost all the copper present in serum, this protein has no essential role in copper transport or metabolism or biliary copper excretion at any stage of human development, as evidenced by

normal copper homeostasis in humans and mice with aceruloplasminemia.¹⁵

Cell Biology

Cellular copper uptake occurs via a polytopic membrane protein termed Ctr1 that is essential for early embryonic development.^{21,22} Ctr1 transports copper across the hepatocyte basolateral membrane in a high-affinity, metal-specific fashion that is dependent on multimerization and endocytosis of this protein^{23,24} (Figure 1). Although uptake is a critical step in the supply of copper to the liver, the continuous accumulation of copper in Wilson disease, despite massive increases in total hepatic copper content, suggests that copper homeostasis is not regulated at this step. Under physiological circumstances, the availability of free intracellular copper is restricted.²⁵ Therefore, after hepatocyte uptake, copper is bound to a family of proteins termed metallochaperones that function to deliver this metal to specific pathways, protecting against intracellular copper chelation.^{26,27} The copper chaperone Atox1 is essential for the trafficking of copper to the hepatocyte secretory pathway through direct interaction with the Wilson disease P-type ATPase, ATP7b.²⁸⁻³⁰ Atox1 contains a single copy of the copper-binding motif MXCXXC, which is also present in the amino-terminus of ATP7b (Figure 2). The binding of Atox1 in this amino-terminal region is required for normal hepatic copper metabolism, as shown by analysis of specific ATP7b mutations in patients with

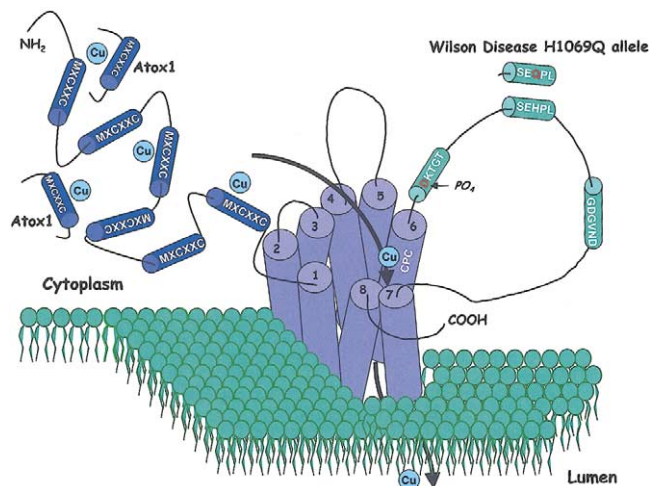


Figure 2. Structural model of the Wilson disease copper-transporting ATPase, ATP7b, illustrating adenosine triphosphate (ATP)-dependent copper transport across the lipid bilayer. Highlighted amino acids regions include MXCXXC copper-binding regions, the DKTGT-containing site of the aspartyl phosphate, the GGVND ATP-binding site, and the CPC copper-binding region in the sixth transmembrane domain. The site of the most common missense mutation (H1069Q) is shown within a SEHPL sequence. Reprinted with permission from the American Society for Biochemistry and Molecular Biology.³⁸

Wilson disease.³⁰ Within the hepatocyte cytoplasm, copper is also found complexed with cysteine-rich proteins termed metallothioneins.³¹ Although they serve no direct role in copper trafficking or homeostasis, metallothioneins may function to protect against the toxicity of this metal under circumstances of copper overload^{31,32} (Figure 1).

ATP7b is a copper-transporting P-type ATPase expressed within the secretory pathway of hepatocytes, and inherited loss-of-function mutations in the gene that encodes this ATPase result in Wilson disease.³³ ATP7b is predominantly located at the trans-Golgi network and functions to transfer copper into the secretory pathway for both incorporation into apoceruloplasmin and excretion into the bile^{33,34} (Figure 1). As the hepatocyte copper content increases, ATP7b cycles to a cytoplasmic compartment near the canalicular membrane, where copper is accumulated in vesicles before biliary excretion.^{35,36} In patients with Wilson disease, the lack of functional ATP7b limits the copper available for incorporation into ceruloplasmin, resulting in secretion of a rapidly degraded apoprotein. The resulting decrease in serum ceruloplasmin concentration is a diagnostic hallmark of this disorder (Figure 1). Although the cell biological mechanisms of vesicular copper movement and excretion at the canalicular membrane of hepatocytes are unknown, recent studies in Bedlington terrier copper toxicosis have identified a small cytosolic protein termed Murr1 that is required for this process³⁷ (Figure 1). A homologous protein has been detected in human liver, suggesting that further analysis of Murr1 function will provide useful insights into this pathway of hepatic copper metabolism.

Several motifs found in all P-type ATPases are present in ATP7b, including an invariant aspartate residue that is the site of the β -aspartyl phosphoryl intermediate required for adenosine triphosphate-dependent copper transport across the lipid bilayer³⁸ (Figure 2). Copper transport requires metal transfer from the amino-terminus to a high-affinity site in the transmembrane channel, accompanied by adenosine triphosphate binding and aspartate phosphorylation.^{34,39} The MXCXXC motifs in the amino-terminus of ATP7b are the site of Atox1 interaction and subsequent copper binding. The most common disease allele found in Northern European populations with Wilson disease is an H1069Q missense mutation found within a conserved SEHPL motif in the cytoplasmic loop between the fifth and sixth transmembrane domains^{40,41} (Figure 2). This mutation results in a temperature-sensitive defect in ATP7b folding and cop-

per-dependent trafficking, suggesting a potential role for this motif in the intracellular localization of ATP7b.^{42,43}

Wilson Disease

Genetics

Wilson disease is observed with a prevalence of approximately 1:30,000, and this is equivalent among all ethnic groups. Although the gene frequency is increased in specific consanguineous populations in which haplotype studies provide evidence for a founder effect, worldwide the heterozygous carrier rate is approximately 1:100, with a disease incidence of 15–25 per million.^{44,45} Molecular analysis of the ATP7b gene in affected patients and families has detected more than 200 distinct mutations, approximately half of which are missense, largely confined to transmembrane domains or well-defined consensus motifs.^{46,47} Databases containing identified mutations are maintained by the University of Alberta (<http://www.uofa-medical-genetics.org/wilson/index.php>) and the Sackler School of Medicine (<http://life2.tau.ac.il/GeneDis/Tables/Wilson/wilson.html>). In populations of Northern European descent, the H1069Q mutation accounts for 40% of the disease alleles, whereas in Asian populations, an A778L mutation within the fourth transmembrane domain occurs in approximately 30% of affected individuals. This degree of allelic heterogeneity means that most affected individuals will be compound heterozygotes, therefore complicating phenotype–genotype analysis. Nevertheless, consistent with the marked clinical variability often observed between affected siblings with Wilson disease, studies in patients homozygous for specific alleles show little correlation between a given mutation and the age of onset, clinical features, biochemical parameters, or disease severity.⁴⁸ Taken together, these data suggest that additional genetic and environmental factors significantly influence the phenotypic outcome of specific mutations in individuals with Wilson disease. For this reason, clinical studies in patients with defined mutations may not be useful in elucidating the physiological details of copper homeostasis.

Pathophysiology

In contrast to these clinical studies, analysis of patient mutations has begun to clarify the molecular pathogenesis of Wilson disease. These studies show specific abnormalities in ATP7b-dependent copper transport, subcellular localization, copper-induced trafficking, and interaction with Atox1.^{30,35,42,43,49–51} This analysis has resulted in a model of disease pathogenesis consistent with the concept that loss of ATP7b function impairs

holoceruloplasmin biosynthesis and biliary copper excretion, with resultant copper-mediated oxidative damage, activation of cell-death pathways, leakage of copper into the plasma, and eventual copper overload in most tissues^{52,53} (Figure 1). Although ATP7b is expressed in many tissues, including the central nervous system, widespread copper accumulation is likely the result of a loss of hepatocyte ATP7b function, because this is reversed after liver transplantation in affected patients.⁵⁴ In this model, the phenotypic heterogeneity observed in patients with Wilson disease could result from genetic and environmental factors that influence copper sequestration by metallothionein, copper delivery to the secretory pathway by Atox1, or copper excretion into bile by Murr1 or homologs of the V-ATPase and Gef1 chloride channel, which play a role in this process in yeast.^{55–57} This model also allows for the possibility that a single mutant ATP7b allele might serve as a risk factor for copper-mediated hepatocyte injury in individuals with more common liver disorders, such as alcoholic cirrhosis.⁵⁸ There are 3 animal models of Wilson disease, including the Long-Evans Cinnamon rat, the toxic milk mouse, and a murine ATP7b gene deletion.^{59–63} Although each develops significant hepatic copper overload, none displays the cirrhosis or neurological disease observed in affected patients; this limits the utility in defining disease pathogenesis and indicates species-specific differences in the genetic and environmental factors that determine the outcome of copper-mediated hepatocyte injury.

Clinical Presentation

If Wilson disease is recognized in time and treated properly, almost all patients may look forward to complete recovery from this otherwise uniformly fatal disorder. For this reason, it is imperative that the disease be considered in the differential diagnosis of any individual with unexplained hepatic or neurological signs and symptoms and that the principles of diagnostic screening and treatment be well understood by anyone caring for such patients. Although copper accumulation may lead to injury in many different tissues, resulting in protean clinical manifestations, most individuals with Wilson disease will present with evidence of liver or central nervous system involvement^{44,54,64} (Table 1). Signs and symptoms of Wilson disease are rarely observed before the age of 3 years, presumably reflecting the considerable capacity of the liver to store excess copper. In children, liver disease is the most common presenting feature, with an average age of 10–13 years—a decade younger than patients presenting with neurological disease.⁶⁵ Approximately 45% of all affected

Table 1. Diagnostic Features of Wilson Disease

Prominent clinical features	
Asymptomatic individual with mild or moderate increases of serum transaminases	
Progressive hepatic cirrhosis with fatigue, anorexia, jaundice	
Chronic active hepatitis with minimal increases of serum aminotransferases	
Rapidly progressive hepatic failure with intravascular hemolysis and splenomegaly	
Parkinsonian features with tremor, bradykinesia, rigidity, and dysarthria	
Personality changes with mood alteration, poor school performance, and impulsive behavior	
Affective disorder, schizophrenia, or psychosis	
Kayser–Fleischer rings (visible) ^a	
Fanconi syndrome with aminoaciduria and glycosuria	
Coombs-negative hemolytic anemia	
Less common clinical features	
Cardiomyopathy and dysrhythmias	
Osteomalacia and arthritis	
Amenorrhea and delayed puberty	
Hypothyroidism and hypoparathyroidism	
Sunflower cataracts and azure lunulae	
Laboratory findings	
Serum ceruloplasmin concentration <20 mg/dL	
Serum copper <100 µg/dL ^b	
Kayser–Fleischer rings (slit-lamp ophthalmoscopic examination)	
Hepatic copper content >250 µg/g dry weight ^{c, d}	
Urinary copper content >100 µg/24 h ^d	
Magnetic resonance imaging/computerized tomography evidence of basal ganglia alterations, subcortical white matter involvement, or atrophy	
Liver biopsy evidence of fatty infiltration and glycogen deposition, micronodular cirrhosis and lymphocytic infiltration, chronic active hepatitis with piecemeal necrosis, and fibrosis	
Molecular genetic analysis with detection of specific mutations in the ATP7b gene	

^aKayser–Fleischer rings rarely visible without slit-lamp examination.

^bFree or non-ceruloplasmin-bound copper (0.05 µmol copper per milligram of ceruloplasmin) is increased.

^cCore size and sampling are critical as error may occur due to uneven distribution of copper in the liver.

^dPrecautions must be taken to avoid contamination from needle, water, or other vehicles.⁴⁴

individuals present with liver disease, 35% with neurological signs and symptoms and 10% with psychiatric disturbances.⁴⁴ The remaining 10% of initial presentations include hemolytic anemia, jaundice, cardiomyopathy, and a number of other less common features, all of which result from copper-mediated tissue injury. In each case, evidence of associated liver dysfunction is detected on further examination (Table 1).

Hepatic involvement in affected patients may take one of several different presentations, each of which can confusingly mimic the features of a variety of acute and chronic liver diseases. These include asymptomatic individuals with increases in the serum transaminases, progressive hepatic cirrhosis, chronic active hepatitis, and rapidly progressive liver failure (Table 1). If the earliest

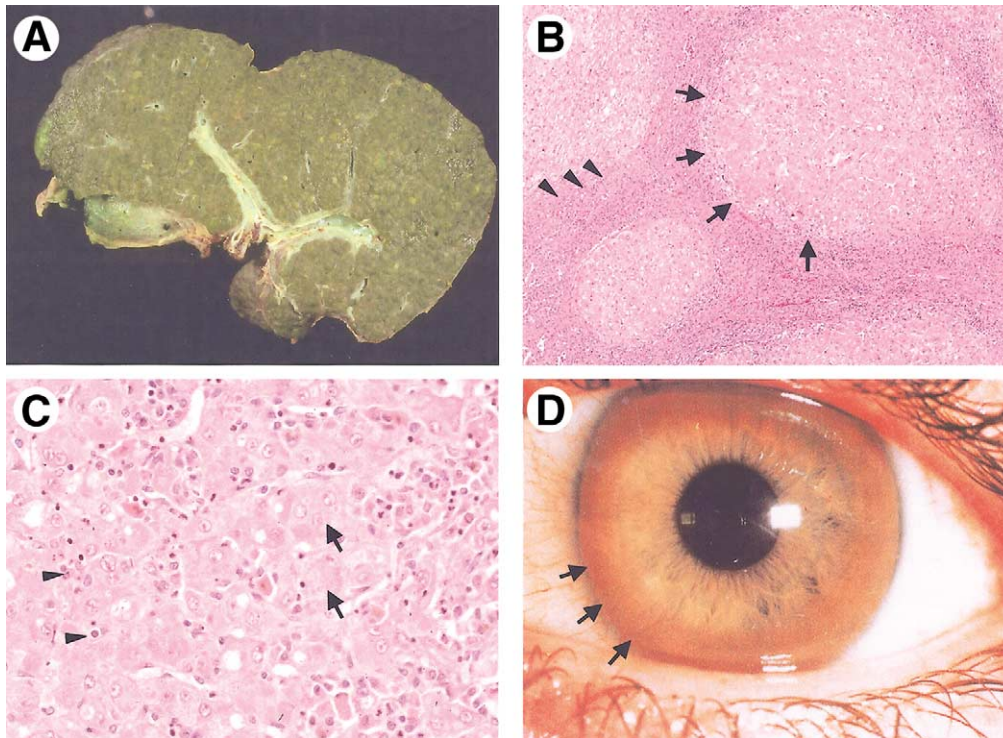


Figure 3. (A) Gross liver pathology in Wilson disease with progressive cirrhosis complicated by fulminant hepatic failure. Firm, nodular tissue is observed over the entire cut surface. (B) Histology from the same liver showing fibrosis (arrowheads) and regenerating nodules (arrows) characteristic of cirrhosis in such patients. (C) Higher magnification within a nodule shows ballooning degeneration of hepatocytes (arrows) and pyknotic nuclei (arrowheads)—these are features of progressive hepatocyte failure. (D) Kayser–Fleischer rings representing copper deposition at Descemet’s membrane (arrows). Provided by Professor Sheila Sherlock and reproduced with permission.⁷⁷

phases of liver disease are not recognized, most patients will inexorably progress to develop cirrhosis and portal hypertension, with associated splenomegaly, ascites, and esophageal varices. In contrast, the presentation in up to 30% of patients is that of chronic active hepatitis with evidence on liver biopsy of significant hepatocellular injury and mononuclear inflammatory infiltrates. Many of these patients will have minimal transaminase increases and no overt features of copper overload. Because it is estimated that Wilson disease accounts for 8%–10% of all chronic active hepatitis in children, this diagnosis must be considered in all such cases in which viral and autoimmune causes have been excluded.^{44,66} In some cases, the initial presentation of affected patients will be rapidly progressive liver failure with evidence of cirrhosis and overwhelming hepatocyte necrosis (Figure 3 A–C). This presentation is usually observed in adolescents, is twice as common in females as males, does not directly correlate with the degree of hepatic copper overload, and is associated with hemolytic anemia and coagulopathy subsequent to the rapid release of copper into the plasma from the liver.^{16,67} The prognosis in such cases is very poor unless liver transplantation is possible.

Irrespective of the initial presentation, all patients with Wilson disease will be found to have abnormalities on liver biopsy.^{68,69} Early changes will be nonspecific and show fatty infiltration and glycogen deposition. Eventually, micronodular cirrhosis may be detected, in some cases with evidence of fibrosis and regenerating nodules

(Figure 3B). The histological picture in chronic active hepatitis is characterized by piecemeal necrosis and fibrosis with inflammatory cell infiltration. Unlike hemochromatosis, progression to hepatocellular carcinoma is rare in patients with Wilson disease.⁷⁰ Kayser–Fleischer rings, arising from copper deposition at Descemet’s membrane, are present in most symptomatic patients and in almost all patients with fulminant hepatic failure but may be absent in those with chronic active hepatitis (Figure 3D). Neurological features, more common in the second or third decade, may initially be subtle but will progress to parkinsonian symptoms, consistent with the neuropathologic findings of basal ganglia involvement.^{71–73} Psychiatric symptoms are also common and include a spectrum from behavioral abnormalities to psychosis^{74–76} (Table 1). As noted previously, a variety of other signs and symptoms reflecting cellular injury from excess copper may be present in affected patients, including Coombs positive hemolytic anemia, cardiomyopathy, and endocrine dysfunction.^{73,77}

Diagnosis and Screening

The diagnosis of Wilson disease is determined by the presence of the signs and symptoms noted previously, in conjunction with laboratory testing that indicates impaired hepatic copper metabolism. Anyone in whom increases of serum transaminases, chronic active hepatitis, or neuropsychiatric symptoms are unexplained or who is found to have Kayser–Fleischer rings should be

Table 2. Screening for Wilson Disease

All siblings and first-degree relatives of affected patients
History (fatigue, anorexia, jaundice, tremor, depression, or new-onset school problems)
Physical examination (Kayser–Fleischer rings, jaundice, splenomegaly, or basal ganglia signs)
Slit-lamp ophthalmoscopic examination (Kayser–Fleischer rings)
Laboratory studies (serum aminotransferases, serum ceruloplasmin, and serum copper)
24-h urine copper
Haplotype or genetic mutation analysis where a proband mutation is identified
Molecular genetic screening in selected populations with frequent common mutation

evaluated for Wilson disease. The serum ceruloplasmin will usually be decreased in affected patients. Because this protein accounts for 95% of the serum copper, measurement of this value will also be abnormally low (Table 1). In contrast, the non-ceruloplasmin-bound copper, defined as the ceruloplasmin-bound copper minus the total serum copper, will often be increased, reflecting release of this metal from the damaged liver.⁷⁷ Ceruloplasmin is an acute-phase protein, and in patients with significant inflammation, as seen in chronic active hepatitis, the serum concentration of this protein may be normal. Although this may present diagnostic difficulty, in most such cases the circulating ceruloplasmin, regardless of concentration, will be devoid of enzymatic activity, reflecting the impaired incorporation of copper during biosynthesis.⁷⁸ Approximately 10% of heterozygotes will have decreased ceruloplasmin and a small increase in hepatic copper content, but these individuals are asymptomatic and present little diagnostic confusion unless they are ill from incidental causes.^{79,80} Patients with aceruloplasminemia present with basal ganglia signs and no detectable ceruloplasmin but are distinguished by normal hepatic copper metabolism and evidence of iron overload.^{12,81} Individuals heterozygous for aceruloplasminemia are asymptomatic but have a half-normal ceruloplasmin concentration that may be diagnostically confusing if liver or basal ganglia symptoms are present from other causes. In such cases, detection of half-normal serum ceruloplasmin in a sibling or parent confirms the presence of a mutant ceruloplasmin allele and rules out the diagnosis of Wilson disease.

The presence of Kayser–Fleischer rings on slit-lamp examination in conjunction with a decreased serum ceruloplasmin concentration in an individual with hepatic or neuropsychiatric symptoms is sufficient to make the diagnosis of Wilson disease. A liver biopsy quantitating hepatic copper content will be useful in circumstances of diagnostic confusion and may also be helpful in assessing

the degree and type of histological injury. It is important to note that a finding of normal hepatic copper content will exclude the diagnosis of Wilson disease. In contrast, neither Kayser–Fleischer rings nor increased liver copper content is individually sufficient to establish the diagnosis of Wilson disease, because either may occur in any disorder with impaired biliary copper excretion.^{44,54,77} Renal filtration of excess free copper in the plasma will increase the urinary copper content in most patients, providing a cost-effective measurement that can be useful in diagnosis and screening (Table 1). Increases in brain copper are detectable by magnetic resonance imaging relatively early in the course of the disease, and this may also prove useful for diagnostic confirmation and for defining specific neurological outcomes to therapy.^{72,82} Although molecular genetic diagnosis has been successfully used in some patients, the degree of allelic heterogeneity at the Wilson locus currently precludes this approach except in circumstances of directed analysis for common or private alleles in individuals from defined populations.^{47,83}

Given the incidence of Wilson disease and the availability of effective prevention and treatment, newborn screening is clearly warranted. Unfortunately, as discussed previously, the developmental physiology of copper metabolism precludes the usefulness of serum ceruloplasmin for this purpose. Therefore, it is currently recommended that screening should be limited to all siblings and first-degree relatives of affected patients. The value of such screening is readily apparent in asymptomatic individuals, in whom prompt initiation of therapy will effectively prevent the otherwise inevitable hepatic and neurological injury. A logical approach to

Table 3. Treatment of Wilson Disease

Chelation therapy
D-Penicillamine: 1–2 g/d PO divided tid ^{a,b}
Trientine: 1–2 g/d PO divided tid ^b
Tetrathiomolybdate: 120 mg/d PO divided in multiple doses ^b
Dietary therapy
Avoidance of copper-rich foods (liver, shellfish, chocolate, nuts, and legumes)
Avoidance of drinking water with copper >1 ppm (0.1 µg/L)
Zinc acetate: 50 mg PO tid ^c
Hepatic transplantation
Orthotopic liver transplantation
Living-related donor transplantation

PO, orally; tid, three times a day.

^aReasonable to use lower doses (1 g) in asymptomatic patients and once copper balance is normalized.

^bPhysical examination, 24-h urine copper, complete blood count, urinalysis, and renal and liver function tests weekly for the first 6 wk, then once a month for the first year.

^cNot recommended as an initial treatment alone in symptomatic patients.

diagnostic screening can be accomplished by using the clinical and laboratory criteria discussed previously (Table 2). Although such an approach will usually permit a conclusive diagnosis, in some circumstances a liver biopsy may be needed to quantitate copper content. If the proband mutation is known, directed molecular genetic analysis is a rapid and reliable approach to screening and may be very useful in individuals in whom chelation therapy has been initiated before an accurate diagnosis is established.^{46,83} In all cases, heterozygous individuals identified through such screening approaches should be offered reproductive and genetic counseling.

Treatment

The therapeutic goal in all patients is to restore and maintain normal copper homeostasis. In most circumstances, this can be accomplished with a number of different oral chelating agents (Table 3). Penicillamine has been shown to effectively ameliorate hepatic and neuropsychiatric signs and symptoms in most patients and to prevent the onset of disease in asymptomatic individuals.^{44,54} Patients show a rapid and dramatic response within the first few months of penicillamine treatment, but poor compliance may result in an acute neurological deterioration, presumably secondary to rapid changes in copper distribution with the central nervous system. Urinary copper excretion can be a useful measure of initial response to treatment and of compliance. Although it is clearly effective, penicillamine does have serious toxicity, including hypersensitivity reactions, bone marrow suppression, and the development of autoimmune disease, and patients must be carefully monitored during treatment. Penicillamine remains the treatment of choice in pregnant patients because considerable experience shows no evidence for teratogenic effects or in utero complications.⁸⁴

Trientine and tetrathiomolybdate are alternative drugs with distinct mechanisms of action that may be also used with similar effectiveness.^{85–87} Sideroblastic anemia and bone marrow suppression are well-described side effects of these medications, and, as with penicillamine, patients must be followed up consistently during treatment. Although dietary restriction alone is of little use in treatment, it is reasonable to suggest to patients that they avoid foods with an abundance of this metal (Table 3). Zinc acetate is a safe and effective treatment to inhibit copper absorption in the gastrointestinal tract and thus maintain neutral or negative copper balance in patients.⁸⁸ As such, zinc treatment alone may be attempted in patients after the return of normal copper balance with chelation treatment.⁵⁴ Existing controversy as to the most appropriate treatment regimen in Wilson disease

largely reflects preferences for specific medications on the basis of experience, because effective treatment is reported with each approach. Details of specific treatment regimens are discussed elsewhere.^{44,64,89} Regardless of the specific approach chosen, in all patients treatment must be continued throughout their lifetime. As such, compliance with medications must be ensured, and careful monitoring for the effectiveness of treatment and any potential side effects should occur at regular intervals (Table 3).

In circumstances of advanced liver failure—from delayed diagnosis, poor compliance with treatment, or rapid, fulminant hepatitis—mortality is almost certain without hepatic transplantation. Wilson disease accounts for 5%–8% of all diagnoses in most major liver transplant programs, and surgeons must therefore be alert for a family history of cirrhosis or neuropsychiatric symptoms in any patient with liver failure of uncertain etiology.^{16,54,90} If successful, liver transplantation will normalize copper homeostasis within 6 months and ameliorate most signs and symptoms of disease.^{16,91–93} Current mortality data show an 85% 1-year survival with excellent long-term prognosis in most patients.⁵⁴ Given this potential outcome, some transplant centers have used living related donors, including heterozygous family members.⁹⁴ Despite these data, the morbidity and mortality of liver transplantation remains substantial, and this approach should be considered as a viable treatment option only in life-threatening circumstances. Liver transplantation is not warranted in patients with advanced and severe neuropsychiatric disease that is unresponsive to chelation therapy, because restoration of copper homeostasis in such cases is not expected to reverse the considerable neurodegeneration that has already occurred from copper toxicity. An excellent and comprehensive practice guideline on Wilson disease has recently been published.⁹⁵

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