

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Diagnosis and Long-Term Management of Wilson Disease

Michael L. Schilsky, MD
Associate Professor of Clinical Medicine
Department of Medicine
Division of Gastroenterology and Hepatology
Center for Liver Disease and Transplantation
Weill Cornell Medical Center

G&H Could you describe the pathophysiology of Wilson disease? Is it a genetic or environmentally triggered condition?

MS Wilson disease is an inherited disease of copper metabolism. It is passed on in an autosomal recessive manner. It occurs in all populations at a rate of approximately 1 in 30,000 individuals, with higher prevalence in populations where there is consanguinity or intermarriage. The underlying pathophysiology for Wilson disease has recently been elucidated by the discovery of the responsible gene, *ATP7B*, that encodes a copper transporting ATPase. This gene product, which is expressed mainly in the liver, is a critical piece of the copper transport pathway in cells. It is important for pushing copper out into bile, which is necessary to achieve homeostasis when excess copper is present. It is also critical for copper incorporation into the protein ceruloplasmin, which is less important in terms of overall copper accumulation but performs other physiologic functions within the body, particularly aiding in the transfer of iron from cells.

Patient with Wilson disease begin accumulating copper at birth, when their normal biliary excretion pathways fail to deliver increased amounts of copper into bile. Thus, dietary copper is absorbed by the gut and taken up by the liver, where it cannot be excreted normally and accumulates, leading to oxidative damage within the liver cells. This injury to the liver is marked by the development of steatohepatitis followed by fibrosis and cirrhosis. Patients who develop accumulations of copper in their livers will

ultimately go through stages of varying durations where they will first manifest changes in liver enzymes and subsequently show signs of advancing liver disease.

Approximately 50% of patients who go on past the second decade of disease will show signs not only of liver disease but also neurologic involvement due to copper accumulation in the central nervous system. The area of the brain most frequently involved is the basal ganglia, which often leads to the development of Parkinson-like symptoms. Copper accumulates in other areas of the brain as well, but this area is seemingly more prone to oxidative injury, and hence the types of symptoms seen in Wilson disease patients are akin to patients with parkinsonism and dystonia.

Very rarely, patients will not manifest disease until later in life, often with variation among siblings, which seems to indicate that disease course is determined not only by genetics but also by environmental factors. These factors may include the dietary intake of copper or other metals such as zinc, which can inhibit the absorption of copper by enterocytes, as well as factors that may affect the individual's ability to resist oxidative injury. There may be other underlying extragenetic differences that predispose some individuals to fibrosis early on, whereas others are more resistant to injury.

There is a fraction of patients who go on to severe acute liver failure due to Wilson disease. This tends to occur within the second and third decades of life and is life-threatening. One hallmark of this presentation is the presence of nonimmune hemolytic anemia along with liver failure. The reason that only a fraction of patients with Wilson disease develop acute liver failure is unknown. However, it is thought that the liver cells receive some insult that causes a drop in reducing potential and resistance to oxidative injury that is so severe that it leads to necrosis and apoptosis of hepatocytes. The only treatment for these patients is immediate liver transplantation, though efforts to reduce circulating copper through plasma exchange, dialysis, or adsorptive methods may buy some time until a suitable organ becomes available.

G&H Could you describe the typical initial presentation of patients with Wilson disease?

MS The typical age of onset for most patients with liver symptoms is within the first or second decade of life. Historically, it was thought that individuals never manifested symptoms before age 4 or 5, but recently patients have been found, through clinical symptoms rather than family screening, as young as 2 years old. At the other end of the spectrum, we have seen patients present in their eighth decade with variable sets of liver and/or neurologic symptoms.

In patients who develop chronic Wilson disease, hepatic and neurologic symptoms tend to be split equally among men and women. However, patients who develop acute liver failure, which is about 5% of all patients with Wilson disease and accounts for 2–5% of all acute liver failures worldwide, are predominantly women. We believe this may be explained by an underlying autoimmune tendency as well as hormonal effects. In animal models of the disease, autoantibodies have developed. Similarly, in animals that have been ovariectomized at a young age, onset of development of severe disease is postponed.

Overall, patients with Wilson disease are divided into two groups, those who are asymptomatic (presymptomatic) and those who are symptomatic. Asymptomatic patients are found either because of abnormal liver function tests without symptoms or, more commonly, by family screening, after a proband has been identified.

G&H What are the treatment options for patients with Wilson disease?

MS Most important is that diagnosis of Wilson disease is established correctly because treatment is lifelong. Once the diagnosis has been made, there are multiple treatment options to choose from. The chelating agents penicillamine (Cuprimine, Aton/Merck) and trientine hydrochloride (Syprine, Aton/Merck) are both effective, and there are no efficacy data that support one over the other. For patients requiring treatment at a very young age, there is reason to consider zinc therapy, as it is a relatively natural treatment. Zinc acts by blocking the enterocyte absorption of copper. For patients who have developed liver injury or more serious physiologic changes, I believe the chelating agents impart a more rapid response. Therefore, in patients who have symptomatic disease, either defined by significant hepatic inflammation or other liver symptoms or neurologic disease, I believe that chelating agents are the first-line therapy. Maintenance therapy can be accomplished with either a reduced dosage of the chelating agents or zinc.

There has been some thought given to using combination therapy, with zinc to inhibit enterocyte absorption of copper along with the chelating agents, which pull copper out of sites in the body where it might be toxic. However, there has never been a study comparing single versus dual therapy, and these must be temporally separated in administration, making for multiple dosages of each per day.

For patients with significant neurologic effects, there is an ongoing study at the University of Michigan using the experimental agent tetrathiomolybdate, which is an avid copper chelator that tends to form complexes with albumin in the circulation that are more inert after they have been bound. Thus far, this agent has been very effective in treating patients with Wilson disease, such that patients do not develop the significant worsening effect experienced by 15–20% of patients on standard chelating agents.

If the disease is already advanced when treatment is started, it may not be possible to halt the natural progression to liver failure or ensuing portal hypertension. In these individuals, standard measures to control portal hypertension, medical or radiologic/surgical, or possibly liver transplantation may be the only option. In treating patients with neurologic disease, there may be worsening despite the initiation of treatment. Some of this worsening may be due to natural disease progression. Some may be due to a sort of “stirring up,” in that copper is removed from some sites in the body and temporarily circulating and available for exchange as the complexes formed by chelating agents may not be entirely inert. In order to avoid this phenomenon, I often start therapy at lower doses and raise them progressively.

G&H Short of transplantation, is there a possibility of salvage therapy in patients with advanced chronic Wilson disease?

MS In patients with associated portal hypertension, ascites, jaundice, or cirrhosis, liver transplant can sometimes be avoided with aggressive medical treatment with careful monitoring. This should be done in concert with a transplant center. When initiating treatment in these individuals, they may have very low albumin levels or raised bilirubin levels and prothrombin time. All of these measures must be monitored to ensure that they are not worsening. Ascites requires diuretic treatment and salt restriction, and varices need either banding or beta blocker therapy as they would in any other liver patient.

Dr. Fred Askari has published on a small series of Wilson disease patients with Child-Pugh System liver scores of 12 or 13, which equate to model for end-stage liver disease (MELD) scores in the low to middle 20s. Dr. Askari was able to achieve significant regression of disease with stan-

standard medical treatment at that time. I have had similar experiences with some of my own patients. Again, these patients require careful monitoring for progression, which, if occurring, is a signal to consider transplantation.

Most scoring systems associated with Wilson disease over the years have at least 2 or 3 parameters that are similar to MELD, and at this point MELD, as monitored at a transplant center, is probably the best indicator of how advanced patients are doing on their therapy. If the MELD score is continually rising, these patients are most likely not going to avoid transplantation. However, even a patient starting with a fairly high MELD score can respond to therapy and avoid progression or even achieve reversal if his or her Wilson disease is successfully controlled.

G&H How can Wilson disease affect a patient's prioritization within the pool of donor organs and liver transplant candidates?

MS Patients with Wilson disease are accorded Status 1, the highest priority, despite their having acute-on-chronic disease that technically has been present since birth. These patients behave as if they had acute liver failure. They suffer the consequences of cerebral edema and impending multiorgan failure and need to be treated in the same manner as others with acute liver failure. They also have the added complication of hemolysis, which contributes to the ongoing perpetuation of the injury, and worsening of renal failure at a more rapid rate due to copper induced renal tubular injury. These are clearly patients that justify a Status 1 transplant. The other categories of patients requiring transplantation are those who present too late and cannot be salvaged with medical therapy. This includes a subset of patients who may be stable but for some reason have been noncompliant with therapy. Sometimes in these individuals, restarting therapy is no longer capable of resisting disease progression, and liver failure may be imminent. Finally, there is the very controversial practice of transplanting for neurologic disease, which some clinicians believe will impart benefit.

In each of these settings, when the liver is replaced, the Wilson disease is in effect cured but the effects of the copper damage outside the liver are not. If a patient has significant, irreparable neurologic injury, it will not improve. However, if they have neurologic disease that is in transition and can be treated medically, the neurologic disease will improve as well. As the pathophysiology of the disease is considered a problem of a mutant protein primarily expressed in hepatocytes, replacement of the liver can be seen as a very gross gene therapy. Thus patients, with rare exception, do not require treatment for their Wilson disease after the transplantation. However, Wilson disease transplant patients should still be differentiated from standard transplant patients, particularly

those with previous neurologic symptoms. These patients have the potential to develop neurologic complications from the standard posttransplant immunosuppressive therapies with calcineurin inhibitors. They also may have worse postoperative outcomes due to an impaired ability to handle secretions and avoid aspiration.

G&H What is the long-term prognosis for patients with Wilson disease who respond to standard medical therapy?

MS Those patients who respond to treatment, even with cirrhosis at the outset, do very well. I tell my patients that they will die with their Wilson disease, not of it. If therapy does remain effective, I prefer to reduce dosage over the years because there are some individuals who are over-treated. When too much copper is removed over time, it can cause the accumulation of iron in the body or reduce blood cell counts. In our standard monitoring of patients, we look at copper status as well as liver function.

G&H Are there any associated conditions or complications of concern in older patients with Wilson disease?

MS Currently, we are treating the first generation of life-long survivors of Wilson disease. Successful treatment for Wilson disease was first done in the 1950s and has been in wide use since the 1960s. We are now seeing patients in their sixth, seventh, and eighth decades of life. Some of their concerns are similar to those seen across the population, whereas others are more unique to their condition. There is a question of whether more frequent bone disease is present in Wilson disease patients because their chronic liver disease may have impaired vitamin D metabolism, and osteoporosis and osteopenia may develop. Patients with neurologic impairment may have dysautonomia, which may result in near-syncope attacks or sudden changes in heart rate. Screening for hepatoma in patients with Wilson disease and cirrhosis seems to be warranted, based on registry data from Europe. Overall, these patients seem to do as well as their peers and are aging gracefully.

Suggested Reading

Brewer GJ, Askari FK. Wilson's disease: clinical management and therapy. *J Hepatol*. 2005;42:S13-S21.

Brewer GJ, Askari FK, Lorincz MT, et al. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Arch Neurol*. 2006;63:521-527.

Ala A, Schilsky ML. Wilson disease: pathophysiology, diagnosis, treatment, and screening. *Clin Liver Dis*. 2004;8:787-805.

Ala A, Borjigin J, Rochwarger A, Schilsky M. Wilson disease in septuagenarian siblings: Raising the bar for diagnosis. *Hepatology*. 2005;41:668-670.