ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Presentations of Wilson Disease

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G&H What is Wilson disease?

MS Wilson disease is a disorder of copper metabolism that occurs in roughly 1 in 30,000 individuals, although some possibility exists that this may be a slight underestimate. It is an autosomal recessive disorder that is the result of mutations to a copper transporter now identified as ATP7B that resides within hepatocytes and other cells but is more highly expressed within hepatocytes of the liver. The function of ATP7B is to move copper from the liver into bile when it is present in excess, as well as to be involved in the incorporation of copper in the biosynthetic process for producing the protein ceruloplasmin, which is a glycoprotein secreted by liver cells into the circulation. In Wilson disease, there is a defect in the function of this ATP7B transporter, such that biliary copper excretion is markedly reduced. When this occurs, over time there is an accumulation of copper within the liver and subsequently within other tissues. This accounts for the order of the disease manifestations in most patients of liver disease first and then neurologic and/or psychiatric manifestations because of copper deposits in other tissues, mainly the central nervous system, that cause injury to the brain.

G&H Could you expand on the spectrum of presentations of Wilson disease?

MS Wilson disease has a wide range of clinical presentations, making it difficult for clinicians to identify this disorder. In the past, this disease has been called a great masquerader because in the beginning it may be silent. Later on, clinicians may find silent liver disease but patients may manifest neurologic or psychiatric disease as their first presenting symptom.

In addition, acute liver failure is an unusual presentation that occurs in approximately 5% of patients with Wilson disease and typically develops in the second decade, although it can occur later on as well. Individuals with this presentation may not have been suspected of any underlying liver disease and suddenly present with severe acute liver failure with associated hepatic encephalopathy, coagulopathy, and nonimmune hemolytic anemia. Often, the majority of these individuals need liver transplantation for their survival.

G&H Could you discuss the clinical features and manifestations of a patient with hepatic presentations of Wilson disease?

MS The patient starts out as an asymptomatic individual who usually develops inflammatory changes detected on biochemical testing, and subsequently goes on to have progressive liver injury with fibrosis and ultimately cirrhosis of the liver with portal hypertension. At this last stage, the patient may develop manifestations (ascites, jaundice, hepatic encephalopathy, and, in small numbers, hepatocellular carcinoma or cholangiocarcinoma) in common with many patients with cirrhosis due to other liver diseases. Thus, patients with hepatic Wilson disease are often indistinguishable from other patients with chronic inflammatory states in the liver.

However, sometimes the patient does not have isolated hepatic manifestations. The patient may occasionally have concurrent neurologic disease, which typically presents as tremors, difficulty with speech, dysarthria, swallowing problems (due to transfer dysphasia), and difficulty in gait and balance. In some patients, the neurologic manifestations may present similar to Parkinson disease, which is not surprising given that the main site

within the brain that is often involved is the basal ganglia. To complicate matters, when patients have chronic encephalopathy and portosystemic shunting, the basal ganglia may also be impacted by other confounders, including hypermanganism. Because these confounders also affect the same part of the brain, they may magnify some of the findings in these individuals.

G&H What are some of the more unusual presentations of Wilson disease that may be missed?

MS Clinicians most often correctly consider Wilson disease when abnormalities are detected in liver function. One of the more unusual presentations of the disease occurs in asymptomatic individuals who have fortuitous findings of Kayser-Fleischer rings, which are cornea deposits of copper and are one of the clinical signs of the disease that occur in approximately 50% of patients with hepatic presentations but in over 95% with neurologic signs or symptoms. In rare instances, these asymptomatic individuals have gone for ophthalmologic examinations where those rings were found, eventually leading to a diagnosis of Wilson disease. Other times, patients may have what seems to be a small tremor. Magnetic resonance of the brain may show changes in the basal ganglia or other findings suggestive of metabolic disease, and a diagnosis of Wilson disease may then be sought.

The other uncommon presentations are typically related to psychiatric disease. There is often at least a 1- to 2-year delay from the onset of psychiatric and neurologic symptoms to the time of diagnosis of Wilson disease. Some of these individuals may have a labile mood, whereas others have more striking symptoms. If mental health problems occur at a young age, they may present as a disturbance in the concentration and ability to perform in school, so an A student may suddenly become a C or D student. There may be interruption of relationships due to the volatile nature of behavior or atypical behavior, including exhibitionism or other disinhibited types of behavior, that may occur. The difficulty is that adolescence is often a time when behavioral changes occur, so Wilson disease must be part of the differential diagnosis, and liver tests have to be examined to begin to put the pieces together.

Wilson disease is also known as a movement disorder, and there are some patients who present with choreiform movements of the hands and other limbs that mimic other diseases. It is unusual to present these symptoms at a young age, but it sometimes does occur.

In addition, among the small percent of individuals with Wilson disease who present with acute liver failure, one of the hallmarks, when it is severe, is nonimmune hemolytic anemia. These patients have jaundice due to a high bilirubin level and have a high indirect bilirubin level due to hemolysis. Patients may be sent to a hematologist if hemolysis is noticed before the severe underlying liver disease. I have seen individuals present with this clinical picture, and only when their international normalized ratio is checked is it realized that they are in liver failure. In addition, nonimmune hemolytic anemia may occasionally occur without liver failure, but the anemia may be thought to be due to an infection or even go unreported as it may be transient.

G&H How does the presentation of Wilson disease vary based on age, genetic mutation, and sex?

MS Presentation is somewhat age-dependent. Epidemiologically, pediatric patients are more likely to be asymptomatic or have just liver disease. Moving toward the adult spectrum, there is more mixed disease, and more of the common neurologic and/or psychiatric presentations and concurrent symptoms are found in older adults.

Presentation of the disease may be very variable even between siblings with the same mutations. For example, one sibling may present with minor liver disease while the other may have advanced cirrhosis, or one sibling may have a mild tremor while the other may have severe neurodegeneration. Analysis of large databases of patients with mutations typically shows that the majority of individuals are compound heterozygotes. That means that they have 2 different mutations on each allele of chromosome 13 that encodes for *ATP7B*. The majority of individuals, especially in the North American population, do not have the same mutations. Even upon analysis of these findings, so far there has not been perfect genotype-phenotype correlation.

Confounding attempts at genotype-phenotype correlation are environmental factors, including the intake of copper or other elements such as zinc, which may alter copper uptake. Other extragenic factors may affect the ability of the liver to deal with the oxidative injury that copper induces, so some patients may be more susceptible to the injury at an earlier time. There is much that is not yet understood regarding the large litany of factors that likely influence ultimate disease expression in these individuals.

With respect to sex, there is an equal split between males and females being affected by Wilson disease. However, interestingly, in patients with Wilson disease who present with acute liver failure, there is approximately a 2- to 4-fold increase in the frequency of women compared to men. It has been suggested that this may, in part, have to do with hormonal changes. In studies of animal models of Wilson disease, when ovariectomies are performed

in female rodents, there is a delay in the presentation of severe injury to the liver, although it still occurs. Another factor may be whether or not those individuals are more subject to autoimmunity, which may play a role in compounding the injury to the liver initially and then accelerating its occurrence.

G&H Is it known how often patients are asymptomatic?

MS Currently, diagnosis of an asymptomatic individual commonly occurs with family screening. When an individual is diagnosed with Wilson disease, all first-degree family members, in particular siblings, are screened. We often may find siblings at a stage before they have developed symptoms. As there is not yet an effective screening test for Wilson disease in the general population, it is not included in the current neonatal screening platforms. However, in the future, DNA-based, biochemical, or immunologic assays may allow for neonatal screening. Such screening would likely shift the curve to a younger age and enable clinicians to identify more asymptomatic individuals.

G&H Why is early recognition of Wilson disease important?

MS Early recognition is critical. If the disease is recognized early, hopefully at an asymptomatic or minimally symptomatic stage, treatment can prevent development or progression of the disease, or if signs or symptoms are present, treatment may be able to reverse them. Wilson disease is one of the diseases of the liver where regression of fibrosis and both histologic and clinical improvement have been seen with effective medical therapy.

G&H What is necessary to establish a diagnosis of Wilson disease?

MS There are many things that can be used to establish a diagnosis. In particular, the Leipzig criteria are a helpful way for clinicians to gauge with findings, both clinical and biochemical, to what degree of probability a patient may have the disease or whether the clinician should continue the evaluation process to eliminate the disease. The Leipzig criteria consider signs and symptoms such as Kayser-Fleischer rings, the level of ceruloplasmin, and the presence of neurologic disease. For patients who undergo liver biopsy, both the histology and quantitative copper of the biopsy can help and are also included in the criteria. Importantly, molecular genetic studies are part of the criteria as well. These studies have become more common and are very informative, as they now allow clinicians to identify mutations of *ATP7B* with high frequency. Thus, molecular testing, along with biochemical, histologic, and other evaluations of patients, allows doctors to confirm the diagnosis as well as obtain a sense of the stage of the liver disease, which is important with respect to prognosis and clinical care of these individuals.

G&H What are the priorities of research in Wilson disease?

MS One priority is neonatal screening. However, most screening tests are only 90% to 95% effective, so clinicians will still need to search for this disease later on in appropriate patients. Another priority is no longer considering survival to be the only endpoint of treatment because medical therapy is lifelong. It is important to consider the effectiveness of treatment as well as the safety of treatment. Patients' quality of life can be enhanced by reducing complications of both therapy and of the disease itself. One of the greatest challenges of lifetime therapy, which is not unique to Wilson disease, is adherence. Therapy currently consists of medications often multiple times a day. Simplification of regimens to once a day is desired and needs to be studied further, as well as potential cures for the disease. Within the next year, gene therapy trials will likely launch, and there may be the potential for gene repair; however, due to the number of disease-specific mutations for *ATP7B*, dominant mutations will be needed to make this a cost-effective strategy.

Disclosures

Dr Schilsky has received grant support from Alexion, GMPO, and the Wilson Disease Association.

Suggested Reading

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