Wilson Disease

Diagnosis, Treatment, and Follow-up

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KEYWORDS

• Wilson disease • Copper • Ceruloplasmin • Liver failure

KEY POINTS

- Consideration of a diagnosis of Wilson disease is still the critical factor in testing for and establishing disease diagnosis.
- In association with other clinical and biochemical tests, liver biopsy results and molecular genetic testing can be used to generate a score for diagnosing Wilson disease.
- Medical therapy is effective for most patients; liver transplant can rescue those with acute liver failure or those with advanced liver disease who fail to respond to or discontinue medical therapy.
- Treatment monitoring must be done at regular intervals and includes clinical evaluation, liver tests and blood counts, and copper metabolic parameters.

INTRODUCTION

Sir Samuel Alexander Kinnier Wilson, the American born and British-trained neurologist for whom this disorder is named, was the first who linked the occurrence of the neurologic degenerative disease with cirrhosis of the liver that was mostly identified at autopsy in his patients. It is now more than a century since the publication of his landmark thesis[1] and there is now a clear understanding of the disease pathophysiology and its underlying genetic defect. This knowledge has led to earlier clinical recognition of disease and improvement in diagnostics useful for generating clinical algorithms and scoring systems to aid clinicians. The focus of this review is to aid practicing gastroenterologists in identify patients with Wilson disease in a timely fashion and allow them to initiate appropriate therapy and treatment monitoring.

Disclosure: Dr. M.L. Schilsky is an investigator for WTX101 trial (Wilson therapeutics, sponsor), advisor for GMPO and Kadmon, serves on the Chair medical advisory committee for the Wilson Disease Association.

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PATHOGENESIS AND EPIDEMIOLOGY

The underpinning mechanism of Wilson disease is a defect in ATP7B, a copper transporting ATPase that is mainly expressed in hepatocytes.[2] This altered function is due to mutation of the *ATP7B* gene, for which there are more than 500 known disease-associated mutations at present. Therefore, in North America, where there is no single dominant mutation, most patients are compound heterozygotes with a different mutation on each allele of the gene that is localized to chromosome 13.[3] The disease is thought to be 100% penetrant but with variable phenotype.

The incidence of Wilson disease is commonly quoted as approximately 1:30,000; however, more recent genetic studies from the United Kingdom question whether there is a higher gene frequency.[4] There are some unique populations where there is an increased disease incidence thought to be related to consanguinity, and here there are often dominant mutations of *ATP7B*.[5,6]

In Wilson disease patients with absent or dysfunctional ATP7B, the normal biliary copper excretion required for copper homeostasis is reduced and copper accumulates in liver cells. This accumulation of copper eventually overwhelms safe storage capacity and cellular injury occurs.[2] The degree of liver disease and timing for its expression is variable in individuals, making this a challenging diagnosis in some patients. The variability is likely due to differences in dietary intake of copper, the natural source for this essential element, and an individual's antioxidant capacity, susceptibility to hepatic fibrosis, and hormonal influences. Evidence for the extragenic influences on disease expression comes from siblings with the same genetic defect that express widely variable phenotypes.[7] In addition, patients may have other hepatic disorders in concert with Wilson disease, and this may accelerate disease progression.[8]

When the liver's capacity for copper storage is exceeded, and when liver cells are injured, copper is released into the circulation and may accumulate in other organs, notably the central nervous system, where it may cause neurologic and psychiatric disease as well as give rise to the characteristic Kayser-Fleischer corneal deposits of copper. Most Wilson disease patients typically present with liver disease during their first and second decades of life. By contrast, patients with neurologic or psychiatric symptoms and disease present in the second and third decades or later on.[9] There are exceptions, however, and patients have been diagnosed with Wilson disease in their eighth decade of life with severe or mild symptoms.[10]

The low level of circulating ceruloplasmin found in most patients with Wilson disease is directly related to defective copper handling in hepatocytes as a result of mutation of *ATP7B*. ATP7B functions in biliary copper excretion but also in moving copper into the trans-Golgi network, the biosynthetic compartment, where the peptide of ceruloplasmin acquires its complement of copper and reaches its final folded state before release into the circulation.[11] Without the normal complement of copper, the peptide folds differently and its circulating half-life is reduced,[12] leading to the phenotypic finding of a low level of ceruloplasmin in the circulation of patients with Wilson disease. A lack of ceruloplasmin by itself does not lead to copper accumulation, as shown by the rare disorder aceruloplasminemia. This disorder results from a defect in the ceruloplasmin gene with a failure of ceruloplasmin synthesis by liver cells, but there is no hepatic copper accumulation, rather iron-induced neurodegeneration.[13,14]

DIAGNOSIS OF WILSON DISEASE

Wilson disease can be diagnosed with increased accuracy given better understanding of the disorder and also the addition of molecular diagnostic testing. Over the years since Wilson made the diagnosis by the recognition of the neurologic findings in his