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The Wilson's disease - etiology, symptoms in various organs, diagnosis, treatment, prognosis

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Abstract

Introduction:

Wilson disease (WD) is a genetic disorder of copper metabolism caused by ATP7B gene mutations, impairing copper excretion and leading to copper accumulation in organs. It affects children and adults, causing liver damage, cirrhosis, neuropsychiatric symptoms, and, if untreated, death. Symptoms, such as Kayser-Fleischer rings, neurological issues, and low serum ceruloplasmin levels, vary widely, complicating early diagnosis. Although rare, WD is one of the few preventable movement disorders, with treatments available to slow disease progression.

Purpose:

This review aims to enhance understanding and management of WD by summarizing current guidelines and offering practical recommendations for clinical practice.

Material and methods:

In our article, we have comprehensively discussed WD. Reviewing the latest literature, we have summarized the symptoms, etiology, diagnosis, treatment and prognosis of this disease.

Discussion:

Wilson disease remains a significant clinical challenge due to its heterogeneous presentation and difficulty in early diagnosis. Despite effective treatments, that can prevent disease progression, many patients experience delayed diagnosis, leading to irreversible organ damage. Advances in genetic testing and biomarkers have improved diagnostic accuracy, enabling earlier detection and better management outcomes. However, nonadherence to lifelong therapy remains a major hurdle, emphasizing the need for ongoing patient education. Emerging therapies and personalized medicine offer promise for improving outcomes and minimizing long-term complications, highlighting the need for continued research and treatment refinement.

Keywords: Wilson disease; ATP7B; ceruloplasmin; Kayser-Fleischer rings.

Introduction:

Wilson disease is an inherited disorder of copper metabolism that affects both children and adults. First described in 1912 by Kinnear Wilson as "progressive lenticular degeneration", WD follows an autosomal recessive inheritance pattern, leading to copper accumulation in various tissues. This copper overload results from mutations in the ATP7B gene, which impair copper excretion. If left untreated, WD can cause a range of systemic manifestations, including liver disease, cirrhosis, neurologic symptoms, psychiatric disturbances, and, in severe cases, death. Although significant progress has been made in diagnosis and treatment over the past century, WD still carries a high risk of disability and mortality, largely due to its rarity, clinical heterogeneity which contribute to delaying the diagnostic process. Treatment nonadherence further complicates disease management, as lifelong therapy is required to prevent progression. [1,2,3]

The key features of WD include liver disease, cirrhosis, neuropsychiatric symptoms, Kayser-Fleischer rings (copper deposits in the eyes), and acute hemolysis, often accompanied by liver failure. WD is not restricted to children or young adults and can present at any age. Diagnosis is typically based on a combination of clinical signs, such as Kayser-Fleischer rings and neurologic symptoms, along with laboratory findings like low serum ceruloplasmin levels (<0.1 g/L). However, due to the wide variation in clinical presentation, diagnosis is often delayed, making awareness of the condition and its management crucial. [1,4]

Despite being a rare disease, WD is one of the few preventable movement disorders, with therapies available that can modify disease progression. This review aims to improve understanding, diagnosis, and treatment of WD by summarizing recent guidelines from the American Association for the Study of Liver Diseases (AASLD) and the latest scientific publications. It also provides practical recommendations for integrating these guidelines into clinical practice and discusses recent advancements in the field. [5, 6]

Purpose:

The purpose of this review is to provide a comprehensive understanding of WD, focusing on its clinical presentation, epidemiology, genetics, pathophysiology, diagnosis, and management. By synthesizing recent advancements and guidelines, particularly those from the American Association for the Study of Liver Diseases, this article aims to improve awareness, facilitate early diagnosis, and optimize treatment strategies for WD. Additionally, it offers practical recommendations for integrating current evidence-based practices into clinical care, addressing challenges such as treatment adherence and the management of systemic complications, to ultimately improve patient outcomes.

Material and methods:

This study presents a systematic review of the current literature on the diagnosis, treatment, and management of Wilson disease. A comprehensive search of databases including PubMed, MEDLINE, and Scopus was conducted to identify relevant peer-reviewed studies, clinical trials, and reviews published from 1912 to 2024. Key terms such as "Wilson disease," "copper metabolism," "chelating agents," and "liver transplantation" were used to gather studies that focused on the clinical aspects of WD . Studies were included if they discussed diagnostic criteria, therapeutic strategies, and patient outcomes, while non-English publications and those lacking original data were excluded. Data extraction focused on clinical management, treatment efficacy, and long-term outcomes, with an emphasis on neurological and hepatic improvements. The findings were synthesized to identify trends and inform the current understanding of WD management.

Etiology:

WD is a rare genetic disorder caused by mutations in the ATP7B gene, located on the long arm of chromosome 13 (13q), which encodes a copper-transporting ATPase primarily expressed in hepatocytes. This defect impairs the body's ability to excrete copper through bile, leading to copper buildup in the liver and, eventually, other organs such as the brain and corneas. Over 500 disease-associated ATP7B mutations have been identified, and most patients, particularly in North America, are compound heterozygotes, meaning they inherit different mutations on each allele of the gene. [1,7]

The global prevalence of WD is estimated at approximately 1 in 30,000 people, with around 8,300–11,000 cases expected in the United States. However, genetic studies in the UK suggest a higher prevalence, potentially as frequent as 1 in 7,026 to 1 in 20,000, indicating that WD may be underdiagnosed. This discrepancy can be attributed to misdiagnosis as other hepatic, neurological, or psychiatric conditions, and to the incomplete penetrance of the gene, where some individuals with mutations may not show severe clinical manifestations. Still, in most fully studied cases, some evidence of phenotypical disease is present. [2,7]

WD typically presents between the ages of 4 and 40, though it has been detected in individuals as young as 3 and as old as 70. It affects males and females equally, across all races and ethnicities. In its early stages, copper accumulates primarily in the liver, leading to various degrees of liver damage. Without proper excretion, copper continues to build up, causing oxidative stress, free radical production, and damage to essential cellular components like proteins, lipids, and DNA. Over time, copper overload spreads to other organs,

particularly the brain and cornea, manifesting in neurological, psychiatric, and ophthalmological symptoms. [2,7]

Copper, an essential trace element, is usually regulated through dietary intake and excretion, primarily via the liver. The liver incorporates copper into ceruloplasmin, a serum protein responsible for copper transport, and excretes excess copper into bile, which is eventually eliminated in the stool. In WD, the malfunctioning ATP7B gene disrupts this process, leading to impaired copper incorporation into ceruloplasmin and reduced biliary copper excretion. This results in lower circulating ceruloplasmin levels and copper buildup. Without treatment, the progressive accumulation of copper can lead to fatal outcomes due to advanced liver disease and other systemic damage. [2,8]

Symptoms:

WD is a systemic disorder caused by copper accumulation in various organs, leading to a wide range of symptoms, particularly in the liver, brain, eyes, and other systems. Because WD mimics many other conditions, it requires a careful differential diagnosis, especially since its symptoms are nonspecific and vary widely. [1,2,3]

Liver-related symptoms can range from asymptomatic cases, often discovered during family screening, to symptomatic presentations such as fatigue, loss of appetite, jaundice, and even severe liver damage. Patients with asymptomatic WD may only show elevated liver enzymes like aspartate aminotransferase and alanine aminotransferase. Symptomatic hepatic cases can progress to acute hepatitis, portal hypertension, hepatomegaly, and cirrhosis. About 3% to 5% of WD patients present with acute liver failure (ALF), often undiagnosed until the onset of severe symptoms like jaundice, hemolysis, coagulopathy, and rapid renal dysfunction. Without liver transplantation, ALF due to WD is nearly universally fatal. [1,8]

Neurological symptoms often manifest around the age of 20 or later, including tremors, muscle stiffness, trouble speaking, and psychiatric symptoms like personality changes, anxiety, and hallucinations. A distinctive feature in advanced neurological cases is the “face of the giant panda” sign on brain MRI. Ocular manifestations, particularly Kayser-Fleischer rings (golden-brown rings around the cornea), are seen in 90% of patients with neurological involvement but are less common in those with hepatic symptoms. Another rare finding is sunflower cataracts, which resemble a sunflower pattern in the eye but do not affect vision and are reversible with treatment. [9, 10]

Beyond the liver and brain, WD can present with hematologic, cardiac, renal, skeletal, and endocrine complications. Hematologic features include hemolysis due to copper-induced damage to red blood cells and conditions like thrombocytopenia and leukopenia linked to

hypersplenism. Renal issues, such as nephrolithiasis, Fanconi syndrome, and hypokalemia, may also occur. Skeletal manifestations, resembling rickets, involve demineralization and muscle weakness. Cardiac complications may include cardiomyopathy, arrhythmias, and atrial fibrillation, while endocrine issues can involve hypoparathyroidism, infertility, and frequent miscarriages. [11]

Due to its diverse clinical presentations, WD requires awareness and timely diagnosis for effective management, as early treatment can modify disease progression and prevent irreversible damage. [10,11]

Diagnosis:

The diagnosis has become more accurate due to advancements in understanding the disease and the introduction of molecular diagnostic tests. Initially identified by neurologic symptoms, diagnostic capabilities have significantly evolved, incorporating liver tests, liver biopsies, and biochemical assays for ceruloplasmin and copper levels. [11,12]

Diagnosing WD is challenging and typically involves a combination of clinical evaluation, blood tests, urine tests, and liver biopsy. Genetic testing can be valuable for screening relatives of affected individuals. The diagnosis is often difficult due to the variability in clinical features and lab results, which include serum ceruloplasmin levels and 24-hour urinary copper excretion. The American Association for the Study of Liver Diseases (AASLD) suggests considering WD in patients with unexplained liver abnormalities, especially when accompanied by neurological or psychiatric symptoms. [13,14]

Timely identification of WD is crucial, particularly in patients presenting with cirrhosis, neurological signs, or Kayser-Fleischer rings, who are more easily diagnosed. However, many patients with liver disease do not meet all diagnostic criteria, complicating the process. Neurological symptoms often emerge later than liver issues but can be the initial signs prompting further investigation. The mean age for symptom onset ranges from 20 to 30 years, but symptoms can appear at any age, necessitating a high index of suspicion among clinicians. [14,15]

When WD is suspected, a comprehensive personal and family medical history should be gathered, along with a thorough physical examination focusing on liver, neurological, and psychiatric conditions. Essential assessments include liver biochemistry, serum ceruloplasmin levels, 24-hour urinary copper excretion, and eye examinations for Kayser-Fleischer rings. While decreased serum ceruloplasmin levels are common in WD, they are not definitive for diagnosis, as many individuals with low levels do not have the disease. Urinary copper

excretion above 100 µg in symptomatic patients and above 40 µg in asymptomatic individuals can indicate WD but require clinical correlation. [2,11]

A multidisciplinary approach is recommended, particularly for eye and neurological assessments. Early differential diagnosis is vital, especially to differentiate WD from conditions like autoimmune hepatitis (AIH), which may present similarly in younger patients. In cases of suspected AIH that is unresponsive to treatment, WD should be ruled out. The complexity increases when patients have multiple liver disease etiologies, such as non-alcoholic fatty liver disease (NAFLD) or alcohol-associated liver disease. [3,15]

In clinical practice, the definition of organ damage in asymptomatic WD hinges on elevated liver enzymes and the presence of liver steatosis or fibrosis. Genetic testing for ATP7B mutations can confirm diagnoses when biochemical tests are inconclusive and facilitate screening for at-risk family members, though it is not strictly necessary for diagnosis. Genetic counseling is recommended to help patients and families understand the implications of testing results. [3,16]

In atypical cases, diagnostic scoring systems may assist in confirming or refuting a WD diagnosis and evaluating the potential for effective treatment. This comprehensive approach underscores the complexity of diagnosing WD and the necessity for heightened clinical awareness and multidisciplinary evaluation. [1, 4, 17]

Treatment:

Once WD is diagnosed, immediate treatment is essential. This includes lifelong medical therapy aimed at managing copper levels and may also involve adjunctive therapies tailored to individual patient needs, such as a low copper diet, and management of portal hypertension, neurological, and psychiatric symptoms. [4,6,10]

WD was one of the first liver diseases effectively treated with drug therapy, beginning with penicillamine in the mid-1950s. However, complacency has set in regarding these treatments. Historical accounts, like a 1940s report on identical twins with WD—one succumbing to decompensated cirrhosis and the other left to cope with his condition—underscore the critical need for timely intervention. [11,15,18]

All newly diagnosed WD patients should receive lifelong therapy. The primary treatment focuses on copper chelation or absorption blockage. Nonadherence to this regimen can lead to new or worsening symptoms, liver failure, and potential liver transplantation. A retrospective analysis of 229 patients demonstrated that early treatment is crucial to prevent progressive liver disease, showing that cirrhosis at diagnosis is a strong predictor of mortality and transplantation needs. Early diagnosis at a precirrhotic stage can improve survival rates. [1]

Dietary guidance has shifted from recommending reduced copper intake to encouraging personalized dietary plans with the help of a registered dietitian. Maintaining copper intake below 0.9 mg/day is advised. [1]

For symptomatic patients, initial treatment should include a chelating agent. While D-penicillamine has historically been the primary treatment, trientine is often preferred due to its better tolerability and was recently approved as a maintenance therapy. Both agents promote copper excretion but have different side effect profiles; trientine is associated with fewer adverse effects. The 2022 approval of trientine tetrahydrochloride was based on a clinical trial that confirmed its efficacy compared to penicillamine. [1,2,3]

Asymptomatic patients also require treatment, often with lower doses of a chelating agent or with zinc, which is now recommended as a first-line therapy for those without significant organ damage. Zinc inhibits intestinal copper absorption and creates a negative copper balance, making it a viable option, particularly for those with renal impairment. [4,17, 20]

Regular monitoring of treatment effectiveness is essential. This includes assessing 24-hour urinary copper excretion and biannual evaluations of liver function, complete blood counts, and urinalysis. Signs of overtreatment or nonadherence must be closely monitored, as these can indicate the need for therapy adjustments. If a patient does not respond to zinc, switching back to a chelating agent may be necessary. [8,14, 21]

Even with effective copper management, adjunctive treatments may be needed for neurological symptoms and complications from liver disease. Medications for managing parkinsonism, dystonia, and chorea are available, and if psychiatric symptoms persist, additional psychotropic medications or therapy may be required. Collaboration with specialists is recommended for comprehensive care. [15,16]

Patients may transition to maintenance therapy after at least one year of effective treatment, which may involve lower doses of chelating agents or full-dose zinc. Monitoring during this transition is critical, particularly in the first few months, to ensure ongoing efficacy and compliance. [2, 6, 22]

In cases where liver cirrhosis develops, procedures like Transjugular Intrahepatic Portosystemic Shunt (TIPS) can help manage complications such as recurrent variceal bleeding, while liver transplantation remains a curative option. [4, 9]

A low copper diet is essential, with recommendations to avoid mushrooms, chocolate, nuts, dried fruit, liver, and shellfish. Physiotherapy and occupational therapy can be beneficial for patients experiencing neurological symptoms. Copper-chelating treatments may take several

months to take effect, making supportive therapies important for managing symptoms like ataxia, dystonia, and tremors. [6,10]

Prognosis:

WD patients who receive appropriate care usually have a good long-term prognosis. Early diagnosis, especially before cirrhosis develops, can improve survival rates and reduce the need for liver transplantation. However, cirrhosis significantly increases the risk of death and liver failure. [23]

Various scoring systems have been proposed to assess prognosis, including the King's College Hospital criteria, which take into account factors such as AST level, bilirubin level, prothrombin time, serum copper level, serum creatinine level, and patient age. A score of 7 or more indicates that the patient should be referred for liver transplantation, as without one they are likely to die within 8 weeks. After liver transplantation, the prognosis is good, with a survival rate of 87% at 15 years. [23,24,25]

Untreated WD has a poor prognosis, with a median life expectancy of 40 years. Most patients die from liver disease, while a minority succumb to complications resulting from progressive neurological deterioration. However, early diagnosis and timely treatment, including liver transplantation if necessary, can lead to a normal life expectancy. Long-term drug therapy effectively reduces neurological and hematological symptoms, although it offers limited benefit in cases of cirrhosis or portal hypertension. In such patients, liver transplantation is essential to restore normal copper excretion and may be life-saving. Neurological symptoms often only partially improve with treatment and in rare cases may even worsen. [26]

The prognosis also depends on the severity of liver failure and neurological involvement, as well as the patient's compliance with drug therapy. In most cases without or with compensated cirrhosis, liver function normalizes after 1 to 2 years of treatment. In contrast, patients with acute liver failure rarely benefit from drug therapy alone, and liver transplantation is usually necessary. [28,28,29,30,31]

Liver transplantation provides satisfactory outcomes for patients. Follow-up studies have shown a one-year survival rate of 79%, with some patients surviving for up to 20 years. Survival rates are higher in patients with chronic advanced cirrhosis than in patients with acute liver failure. [28,28,29,30,31]

In general, patients who receive appropriate care for WD have a good long-term prognosis. However, cirrhosis increases the risk of death and liver disease. Early diagnosis, at the precirrhotic stage, may prolong survival and reduce the need for liver transplantation.

Conclusion:

In conclusion, early consideration of WD as a differential diagnosis remains paramount to achieving timely and accurate identification of the condition. Comprehensive diagnostic approaches including clinical evaluation, biochemical testing, liver biopsy, and molecular genetic testing enable precise scoring systems that guide diagnosis and management. For most patients, medical therapy offers effective control of the disease, while liver transplantation remains a critical option for those with acute liver failure or refractory hepatic disease.

WD is caused by mutations in the ATP7B gene and presents as a complex autosomal recessive disorder with diverse clinical manifestations, spanning hepatic, neurologic, psychiatric, and hematologic symptoms. Early diagnosis, particularly in asymptomatic individuals, is associated with significantly better outcomes, underscoring the importance of heightened clinical awareness and robust screening protocols. Ongoing advancements in diagnostic techniques and therapeutic interventions continue to improve the prognosis and quality of life for affected individuals.

DISCLOSURE

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