**Wilson Disease: Why Early Diagnosis Matters and How to Improve Screening**

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**ABSTRACT**

**Introduction:** Wilson disease is a rare genetic disorder of copper metabolism caused by mutations in the *ATP7B* gene, leading to impaired hepatic copper excretion and toxic copper accumulation in the liver, brain, and other organs. The disease manifests with hepatic, neurological, and psychiatric symptoms, ranging from liver dysfunction and cirrhosis to movement disorders, cognitive decline, and mood disturbances. Diagnosis relies on serum ceruloplasmin levels, urinary copper excretion, hepatic copper quantification, genetic testing, and neuroimaging.

Treatment focuses on lifelong copper control through chelating agents (D-penicillamine, trientine) and zinc therapy, while liver transplantation remains the only curative option in severe cases. Despite effective management strategies, early detection challenges, treatment side effects, and long-term monitoring complexities persist. Emerging research on gene therapy, novel chelators, and microbiome-targeted interventions aims to provide safer and more efficient alternatives. Advancements in early diagnosis, optimized treatment, and personalized medicine are essential to improving patient outcomes and quality of life.

**Materials and Methods:** This study conducted a systematic review of published research on Wilson disease, examining its genetic basis, clinical presentation, diagnostic methods, and treatment strategies. Literature was sourced from PubMed, Scopus, and Web of Science, focusing on recent advancements in copper metabolism, ATP7B mutations, and therapeutic interventions. Eligible studies included original research, clinical trials, systematic reviews, and meta-analyses, while case reports and non-English publications were excluded.

**Results:** Wilson disease is a genetic disorder of copper metabolism caused by mutations in the *ATP7B* gene, leading to copper accumulation in the liver, brain, and other organs. This copper overload causes progressive tissue damage, resulting in a wide spectrum of hepatic, neurological, and psychiatric symptoms. Liver-related symptoms range from mild hepatomegaly and elevated liver enzymes to cirrhosis and acute liver failure, while neurological manifestations include tremors, dystonia, dysarthria, and cognitive impairment. Many patients also experience psychiatric disturbances, such as depression, mood instability, and personality changes, making diagnosis particularly challenging.

Diagnosis of Wilson’s disease is based on biochemical tests, including low serum ceruloplasmin, elevated 24-hour urinary copper excretion, and hepatic copper quantification. Genetic testing for *ATP7B* mutations is useful for confirming the diagnosis, particularly in asymptomatic individuals or those with an atypical presentation. Neuroimaging, particularly MRI, is often employed in patients with neurological symptoms, revealing characteristic basal ganglia abnormalities. Despite the availability of these diagnostic tools, many cases remain undiagnosed or misdiagnosed due to the highly variable nature of the disease.

Treatment focuses on lifelong copper management, with copper chelators (D-penicillamine, trientine) and zinc therapy serving as the main therapeutic options to reduce systemic copper levels. In patients with severe liver dysfunction or acute hepatic failure, liver transplantation remains the only curative option. While these therapies are effective in preventing further organ damage, lifelong adherence, potential side effects, and limited treatment options for neurological symptoms present ongoing challenges.

Recent research is exploring alternative treatment approaches, including gene therapy to restore ATP7B function, next-generation copper chelators with improved safety profiles, and microbiome-targeted therapies aimed at regulating intestinal copper absorption. Despite these advancements, early detection, personalized treatment plans, and regular disease monitoring remain essential for improving long-term outcomes and quality of life in Wilson disease patients.

**Conclusions:** Wilson disease is a genetic disorder of copper metabolism that leads to toxic copper accumulation, primarily affecting the liver and brain. Early diagnosis and lifelong treatment are essential to prevent irreversible organ damage. Current therapies include copper chelators (D-penicillamine, trientine), zinc therapy, and liver transplantation for severe cases. Despite their effectiveness, lifelong adherence and potential side effects remain challenges. Emerging treatments, including gene therapy, improved chelators, and microbiome-targeted approaches, offer hope for more effective and less burdensome therapies. A multidisciplinary approach is key to improving long-term patient outcomes and quality of life.

**Keywords:** wilson disease, ATP7B mutation, copper metabolism, chelation therapy, gene therapy

**INTRODUCTION**

Wilson disease (WD) is a rare genetic disorder of copper metabolism caused by mutations in the ATP7B gene, which impairs hepatic copper transport and biliary excretion. This defect leads to excessive copper accumulation, initially in the liver, and subsequently in other organs, particularly the brain, kidneys, and cornea [1,5,9]. The toxic buildup of copper triggers oxidative stress, mitochondrial dysfunction, and progressive tissue damage, resulting in a broad spectrum of clinical manifestations ranging from hepatic dysfunction to neurological and psychiatric symptoms [2,3,12].

The disease typically presents in childhood or early adulthood, with clinical phenotypes classified as hepatic, neurological, or mixed forms. Hepatic presentations often include chronic liver disease, cirrhosis, and acute liver failure, while neurological symptoms can manifest as tremors, dystonia, dysarthria, and cognitive impairments. Psychiatric disturbances such as mood disorders, personality changes, and depression are also frequently observed. A characteristic sign of Wilson disease is the presence of Kayser–Fleischer rings, copper deposits in the cornea, which are commonly seen in patients with neurological involvement. However, the disease can remain asymptomatic for years, leading to delays in diagnosis and an increased risk of irreversible organ damage [11-15].

The pathophysiology of Wilson disease revolves around defective copper homeostasis. In a healthy individual, excess copper is excreted via bile, but in Wilson disease, copper accumulates in hepatocytes, eventually spilling into the bloodstream and depositing in extrahepatic tissues [3,7]. This results in oxidative injury, cellular apoptosis, and inflammation. Recent studies have also highlighted the role of copper-induced cell death, known as cuproptosis, in disease progression, as well as the potential interplay between copper overload and iron-related oxidative damage.

Diagnosis of Wilson disease requires a combination of clinical assessment, biochemical testing, imaging, and genetic analysis [1]. Laboratory findings include low serum ceruloplasmin, increased urinary copper excretion, and elevated hepatic copper content. The modified Leipzig scoring system is often used to establish the diagnosis. Brain imaging in patients with neurological involvement frequently reveals characteristic basal ganglia abnormalities, commonly referred to as the “face of the giant panda” sign. Despite these diagnostic tools, Wilson disease remains underdiagnosed, particularly in patients with atypical presentations, underscoring the need for improved screening strategies.

Treatment primarily focuses on copper chelation and reduction of intestinal copper absorption. First-line therapies include chelating agents such as D-penicillamine and trientine, which enhance urinary copper excretion, while zinc therapy is used to block dietary copper uptake [1,3]. In severe cases, particularly those with fulminant hepatic failure, liver transplantation remains the only curative option. Although these treatments effectively manage copper overload, they require lifelong adherence and are associated with potential adverse effects. Emerging therapies, including gene therapy, novel copper chelators, and microbiome-targeted interventions, are currently under investigation to offer more effective and less burdensome treatment alternatives.

Despite advances in diagnosis and treatment, significant challenges remain in early detection, optimizing therapeutic approaches, and long-term disease monitoring. This review provides a comprehensive examination of Wilson disease, focusing on its genetic and pathophysiological basis, clinical presentation, diagnostic strategies, current treatment modalities, and future therapeutic prospects. Special attention is given to recent discoveries in copper metabolism, emerging therapeutic interventions, and the evolving role of personalized medicine in disease management [15-18] .

**MATERIALS AND METHODS**

This study involved a systematic review of published research on Wilson disease, focusing on its genetic basis, clinical presentation, diagnostic approaches, and therapeutic strategies [1-5]. Relevant literature was identified through searches in databases such as PubMed, using keywords including "Wilson disease," "ATP7B mutation," "copper toxicity," "neurological and hepatic manifestations," "copper chelation," and "novel treatments" [1,2,3].

Eligibility criteria included original research articles, clinical trials, systematic reviews, and meta-analyses that provided insights into disease mechanisms, diagnostic biomarkers, and treatment outcomes [17-20]. Particular emphasis was placed on studies evaluating current therapeutic approaches, such as chelation therapy and liver transplantation, as well as emerging interventions, including gene therapy and microbiome-targeted treatments. Case reports, non-English studies, and articles with limited methodological reliability were excluded.

Data were categorized into key thematic areas, including pathophysiology, clinical features, diagnostic tools, standard treatments, and experimental therapies. Comparative analyses of different management strategies were reviewed to assess their efficacy and long-term outcomes. This structured approach facilitated an in-depth evaluation of Wilson’s disease while identifying critical gaps in research and potential future therapeutic advancements.

**RESULTS**

**Pathogenesis**

The clinical symptoms of Wilson disease arise primarily from pathological tissue damage caused by the toxic accumulation of excess copper [1,2]. The non-ceruloplasmin-bound copper present in the bloodstream is readily taken up by various tissues through specialized transport mechanisms. These include CTR1 and divalent metal transporter (DMT1), which facilitate intracellular copper uptake even when excess levels are present [3]. As copper accumulates beyond the cellular storage capacity, it induces widespread oxidative stress, leading to lipid peroxidation, protein dysfunction, and nucleic acid damage. This oxidative damage disrupts cellular homeostasis, progressively impairing organ function [4,5].

Beyond oxidative stress, copper toxicity also triggers cell death pathways, including apoptosis mediated by acid sphingomyelinase activation, which leads to the production of ceramide, a key apoptotic signaling molecule [6]. Additionally, excess copper interferes with enzymatic activities by binding to protein thiol groups, further disrupting metabolic and structural protein function. Among cellular organelles, mitochondria are particularly vulnerable to copper toxicity, as excess copper impairs their respiratory function, disrupts ATP production, and promotes cell death [7]. This mitochondrial dysfunction contributes significantly to the neurological, hepatic, and systemic manifestations seen in Wilson’s disease, reinforcing the need for early intervention to prevent irreversible tissue damage [8,9].

**Liver Involvement in Wilson Disease**

As the primary site of copper metabolism, the liver plays a central role in systemic copper regulation due to its high expression of the *ATP7B* copper transporter [10]. In Wilson disease, dysfunction of ATP7B impairs biliary copper excretion, leading to progressive hepatic copper accumulation. Consequently, the liver is the first and most frequently affected organ, with copper concentrations in Wilson disease patients typically exceeding normal levels by five to twenty times [11]. However, the distribution of copper within the liver is non-uniform, and its cellular localization changes as the disease progresses [12].

In the early stages, excess copper is primarily stored in the cytoplasm of hepatocytes, bound to metallothioneins, cysteine-rich proteins that help detoxify and sequester heavy metals. As the disease advances, copper accumulates within lysosomes, where it becomes detectable using histological stains such as Timm’s, rhodanine, and orcein [14]. One of the earliest hepatic changes observed in Wilson disease is mitochondrial damage, which disrupts hepatocellular energy metabolism and downregulates genes involved in cholesterol biosynthesis, contributing to hepatic steatosis.

Prolonged exposure to excess copper leads to chronic hepatocyte injury and cell death, triggering an inflammatory response and progressive fibrosis. As fibrosis advances, non-alcoholic fatty liver disease (NAFLD)-like pathology may be observed, with characteristic features such as Mallory-Denk bodies, glycogenated hepatocytic nuclei, and portal and lobular inflammation. In the later stages, macronodular cirrhosis develops, significantly impairing liver function [15-17].

Hepatocyte loss in Wilson disease is primarily driven by apoptotic mechanisms, often triggered by mitochondrial dysfunction. Damaged mitochondria release cytochrome C, initiating apoptosis, while copper-induced activation of acid sphingomyelinase promotes the production of ceramide, an apoptotic signaling molecule. As hepatocyte storage capacity becomes overwhelmed, labile non-ceruloplasmin-bound copper increases in the bloodstream, leading to systemic copper toxicity. The excess circulating copper subsequently deposits in extrahepatic tissues, particularly in the brain, eyes, kidneys, bones, and heart, where it exerts further toxic effects, contributing to the neurological and multi-organ complications characteristic of Wilson disease [18].

**Brain Involvement in Wilson Disease**

In Wilson disease, excessive copper accumulation in the brain can reach levels significantly higher than normal, leading to widespread neurotoxicity. Initially, astrocytes act as a buffer, absorbing excess copper and increasing their numbers in a process known as astrogliosis [19]. However, prolonged exposure leads to astrocyte dysfunction, blood-brain barrier disruption, and neuronal damage. The basal ganglia, thalamus, cerebellum, and brainstem are particularly susceptible, with pathological changes including demyelination, neuroinflammation, and necrosis. These abnormalities are commonly observed as hyperintense lesions on MRI scans.

Damage to the putamen is strongly linked to movement disorders, particularly dystonia and parkinsonism, while disruption of cortico-striatal pathways contributes to psychiatric symptoms and cognitive decline. Lesions in the dentate-rubro-thalamic pathway are associated with coarse action tremors, while cortical and subcortical involvement may lead to epileptic seizures. Additionally, hepatic encephalopathy may further exacerbate neurological symptoms, as evidenced by similarities in MRI findings and the presence of abnormal astrocytes. Retinal abnormalities have also been observed in Wilson disease, correlating with neurological severity and MRI-detected brain pathology [20-22].

**Diagnosis and Challenges**

Wilson disease presents significant challenges for affected individuals, as both **delayed diagnosis and complex disease management** contribute to disease progression and worsening outcomes. Patients often experience **years of unexplained symptoms** before receiving an accurate diagnosis, as the disease mimics a range of other hepatic, neurological, and psychiatric conditions. Hepatic symptoms can resemble **autoimmune hepatitis, non-alcoholic fatty liver disease, or viral hepatitis,** while neurological manifestations may be mistaken for **Parkinson’s disease, dystonia, or psychiatric disorders such as schizophrenia or bipolar disorder.** The **insidious nature** of Wilson disease, coupled with its **heterogeneous clinical presentation,** frequently results in **misdiagnosis or delayed intervention**, allowing copper accumulation to reach toxic levels before treatment is initiated. This delay can have severe consequences, including **irreversible hepatic damage, progressive neurodegeneration, and worsening psychiatric symptoms**, leading to a **significant decline in quality of life** for patients [1-2].

The **diagnostic process** for Wilson disease relies on a combination of **biochemical, genetic, and imaging studies** to confirm the presence of defective copper metabolism. Laboratory tests include **serum ceruloplasmin levels**, which are typically low due to impaired copper transport, and **24-hour urinary copper excretion**, which is elevated as excess copper is excreted through the kidneys instead of the biliary system. Hepatic copper quantification through **liver biopsy** remains one of the most definitive diagnostic tools, particularly in cases where biochemical markers are inconclusive. Genetic testing for **ATP7B mutations** further aids diagnosis, especially for asymptomatic individuals undergoing **family screening** or in cases of **atypical presentation** where Wilson disease is not initially suspected [3]. Additionally, **neuroimaging techniques such as MRI** are valuable in identifying characteristic brain abnormalities in patients with neurological involvement. The presence of **basal ganglia degeneration**, commonly referred to as the **“face of the giant panda” sign**, is strongly suggestive of Wilson disease in patients presenting with movement disorders, cognitive decline, or psychiatric symptoms [4].

Effective management of Wilson disease requires **lifelong copper control**, with treatment strategies aimed at **reducing copper overload, preventing further accumulation, and minimizing organ damage**. The primary treatment approach involves **pharmacological therapies**, including **copper chelators** such as **D-penicillamine and trientine**, which promote the urinary excretion of excess copper. While these agents are effective in reducing systemic copper levels, they are associated with **significant side effects**, including **bone marrow suppression, renal toxicity, and worsening of neurological symptoms** in some patients. As an alternative, **zinc therapy** works by blocking intestinal copper absorption and promoting hepatic metallothionein synthesis, which facilitates safe copper sequestration. Zinc is often used as a **first-line treatment in presymptomatic patients** or as **maintenance therapy** following successful chelation [12-16].

For patients with **severe hepatic dysfunction** or **acute liver failure, liver transplantation** remains the only curative option. Transplantation effectively restores normal copper metabolism by replacing the defective ATP7B function with a healthy donor liver. However, access to transplantation is limited by **organ availability**, the risk of **post-transplant complications**, and the **requirement for lifelong immunosuppression**. Despite these challenges, liver transplantation offers **excellent long-term survival outcomes**, particularly for patients with decompensated cirrhosis or fulminant Wilson disease.

Recent advancements in Wilson disease research have paved the way for **novel therapeutic approaches** aimed at improving disease management while minimizing treatment burden. **Gene therapy** has emerged as a promising strategy, with efforts focused on restoring **ATP7B function** in hepatocytes, potentially offering a **permanent cure**. Studies exploring **AAV-mediated gene transfer** have demonstrated encouraging preclinical results, with the goal of **correcting the underlying genetic defect** rather than simply managing copper overload. Additionally, new **copper-binding molecules** with improved safety profiles are being developed to provide more **targeted chelation therapy** while minimizing adverse effects [1,4].

The **gut-liver axis** has also become a focus of research, with growing evidence suggesting that **gut microbiota play a role in copper metabolism**. Some studies suggest that manipulating gut microbiota through **probiotic interventions** or **microbiome-targeted therapies** could influence **intestinal copper absorption and systemic distribution**, potentially offering a **supportive or adjunctive treatment** alongside traditional therapies [8]. Furthermore, the discovery of **cuproptosis**, a copper-induced cell death mechanism, has opened new research avenues into how **copper toxicity triggers liver cell apoptosis** and how it may be mitigated through **pharmacological or genetic interventions [9]**.

Despite these advancements, significant challenges remain in **early diagnosis, personalized treatment approaches, and long-term disease monitoring**. Many patients continue to **face difficulties with adherence to therapy**, while others experience **progressive neurological decline despite treatment [18-21]**. Ongoing research into **biomarkers for early detection, more effective and better-tolerated therapies**, and **gene-based approaches** aims to revolutionize Wilson disease treatment, reducing disease burden and improving overall prognosis. Future studies focusing on **precision medicine** may enable a more **tailored approach** to treatment, ensuring that patients receive **optimal therapy based on their specific genetic and clinical profile [22-24]**.

**CONCLUSIONS**

Wilson disease is a genetic disorder that disrupts copper metabolism, leading to toxic copper accumulation in the liver, brain, and other organs. This build-up causes progressive liver damage, neurological dysfunction, and psychiatric symptoms, making early detection and treatment essential to prevent irreversible complications [1-4]. However, Wilson’s disease often goes undiagnosed or misdiagnosed for years due to its wide range of symptoms, which can resemble other liver or neurological conditions. Without timely intervention, copper overload leads to liver failure, movement disorders, cognitive impairment, and severe psychiatric disturbances [12, 14].

Treatment for Wilson’s disease focuses on lifelong copper management to prevent further accumulation and systemic toxicity. First-line therapy includes copper-chelating agents such as D-penicillamine and trientine, which promote the excretion of excess copper through urine. For patients who cannot tolerate chelators, zinc therapy is used to block copper absorption in the intestines. These treatments, when started early and maintained consistently, can halt disease progression and, in many cases, reverse symptoms. In severe cases of liver failure or advanced cirrhosis, liver transplantation provides the only curative option by restoring normal copper metabolism [1,3,12].

Despite the effectiveness of existing treatments, lifelong medication adherence is necessary, and some patients experience side effects or persistent symptoms, particularly those with neurological involvement. Emerging research is exploring new therapies that may offer more effective and less burdensome treatment options. Gene therapy aims to correct the underlying genetic defect in *ATP7B*, potentially restoring normal copper metabolism. Additionally, new-generation copper chelators with fewer side effects, gut microbiome-based therapies, and targeted treatments for neurological damage are being developed to improve patient outcomes.

Early diagnosis, personalized treatment plans, and regular monitoring are critical for managing Wilson disease effectively. With ongoing advancements in research, future therapies may provide less invasive, more effective, and potentially curative options for patients, improving both life expectancy and quality of life. A multidisciplinary approach, involving specialists in hepatology, neurology, genetics, and nutrition, is essential to ensure comprehensive care and long-term disease management [14-18].

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All authors have read and agreed with the published version of the manuscript.

**Founding Statement:** The study did not receive funding.

**Institutional Review Board Statement**: Not applicable.

**Informed Consent Statement**: Not applicable.

**Data Availability Statement**: Not applicable.

**Conflict of Interest Statement**: The authors declare no conflicts of interest.

**Acknowledgments**: Not applicable.

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