Advancements in the Diagnosis and Treatment of Wilson's Disease: A Comprehensive Review of Clinical Approaches and Molecular Insights

Raed mohammed alomair [1*], Tallah Ibrahim Alkiady [1], Abdullah Abdulrahman Alkhamees [1], Hamdan Ali Al Alyani [1], Sultan Safah A Alharbi [1], Amira Yousef Ali Aldalili [1], Khalid Obid Abdullah Alruki [1], Basim Othman Nasser Almarshed 1, Mohammed Menwer Alruwaili [1], Taleb Ghazi Thaar Aldalbahi [1], Hatim Bunaydir Bader AImutairi [1], Abdullah Hassan Abdullah Aldawsari [1], Mohammed Mesfer Musaed AL khathami [1], Amer Hassan Mohammed Al-Shahri [1], Hassan Duairam Thawab Al-Shahrani [1]

Abstract

Background: Wilson's disease (WD) is a genetic disorder caused by impaired copper metabolism, leading to copper accumulation in various organs, including the liver, brain, and corneas. Despite early recognition of its clinical symptoms, the diagnosis and management of WD remain challenging due to its diverse presentation and involvement of multiple organ systems. Recent advancements in molecular genetics, early diagnosis, and management have improved patient outcomes. Methods: A systematic review of recent literature was conducted to evaluate the latest clinical guidelines, diagnostic criteria, and therapeutic approaches for Wilson's disease. Studies included clinical trials, case reports, and meta-analyses published from 2015 to 2023, focusing on diagnostic biomarkers, treatment regimens, and long-term prognosis. Results: Early detection of WD remains crucial for preventing irreversible organ damage, especially neurological impairments. Molecular testing, including ATP7B mutation analysis, plays a pivotal role in confirming diagnosis. Chelating agents such as penicillamine and zinc therapy continue to be the mainstay of treatment, although emerging therapies, including gene therapy and novel chelators, show promising results. Liver transplantation remains a critical intervention for patients with advanced liver disease or severe neurological manifestations. The importance of personalized medicine, considering individual genetic and environmental factors, is gaining recognition in optimizing treatment plans. Conclusion: While significant progress has been made in understanding and treating Wilson's disease, challenges remain, particularly in early diagnosis and managing neurological symptoms. Continued research into genetic therapies and more effective treatment regimens is needed to improve long-term outcomes for patients with Wilson's disease. Early intervention, personalized care, and regular monitoring are essential to prevent irreversible damage and enhance the quality of life for affected individuals.

Keywords: Wilson's disease, Diagnosis, Treatment, Molecular Mechanisms, Clinical Guidelines

Significance | This review provides crucial insights into the diagnosis, clinical management, and molecular mechanisms of Wilson's disease.

*Correspondence. Raed mohammed alomair, Ministry of National Guard Health Affairs, Prince Mutib Ibn Abdullah Ibn Abdulaziz Rd, Ar Rimayah, Riyadh 11426, Saudi Arabia
E-mail: akrmesmail2060@gmail.com

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Introduction

Wilson disease, also known as hepatolenticular degeneration, is a rare, autosomal recessive genetic disorder characterized by the pathological accumulation of copper in the body. This condition

Author Affiliation.
[1] Ministry of National Guard Health Affairs, Prince Mutib Ibn Abdullah Ibn Abdulaziz Rd, Ar Rimayah, Riyadh 11426, Saudi Arabia

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primarily affects the liver and brain but can also impact other organ systems, leading to a wide spectrum of clinical manifestations. The disease arises from mutations in the ATP7B gene, located on chromosome 13q, which encodes a copper-transporting ATPase. This enzyme plays a critical role in the excretion of copper into bile for elimination. In Wilson disease, mutations in ATP7B result in a defective protein that impairs copper transport, leading to its toxic buildup in various tissues (Liu et al., 2021). The accumulation of copper, particularly in the liver and basal ganglia, disrupts normal organ function and causes progressive damage if left untreated. Without timely intervention, Wilson disease can be fatal, underlining the importance of early diagnosis and appropriate treatment (Socha et al., 2018).

The clinical presentation of Wilson disease is heterogeneous and highly variable, depending on the stage of the disease and the organs affected. Hepatic symptoms are often among the first to appear and may manifest as vague signs such as vomiting, weakness, ascites, leg swelling, jaundice, and pruritus (Hedera, 2019). These early hepatic symptoms are often followed by neurological manifestations, including tremors, muscle rigidity, dysarthria, and more severe psychiatric disturbances such as personality changes, anxiety, and hallucinations. The progression from hepatic to neurological symptoms reflects the systemic nature of the disease and the critical importance of early detection. However, the variability in clinical features often complicates diagnosis, as patients may present to different specialists, such as hepatologists, neurologists, and psychiatrists, depending on the predominant symptoms (Table 2). Furthermore, the presence of neuropsychiatric symptoms can delay diagnosis, as they often overlap with common psychiatric disorders (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition [ESPGHAN], 2012). Thus, recognizing the subtle early signs of Wilson disease is challenging, and many patients experience delays in diagnosis, which can lead to irreversible organ damage.

The pathophysiology of Wilson disease is intricately linked to the genetic defect in the ATP7B gene. This gene mutation results in the defective copper-transporting ATPase enzyme, which is essential for maintaining copper homeostasis. In healthy individuals, copper absorbed from the diet is incorporated into ceruloplasmin or stored in the liver for excretion. In Wilson disease, the inability of the ATP7B enzyme to effectively transport copper into the bile leads to its accumulation within the hepatocytes. Over time, this excess copper spills over into the bloodstream, where it is deposited in extrahepatic tissues such as the brain, kidneys, and cornea (Lutsenko et al., 2019). The basal ganglia of the brain, responsible for motor control, is particularly vulnerable to copper deposition, leading to the characteristic neurological signs seen in patients with Wilson disease. The deposition of copper in the cornea can also lead to the formation of Kayser-Fleischer rings, which can serve as an important diagnostic clue in patients with neurological or psychiatric symptoms.

The onset of Wilson disease can vary significantly between individuals, with hepatic symptoms typically appearing in childhood or adolescence. Early hepatic signs may include asymptomatic hepatomegaly, hepatitis, or acute liver failure (Członkowska et al., 2018). In contrast, neurological symptoms often emerge later, during the third or fourth decade of life, and are initially subtle, presenting as motor dysfunctions or psychiatric disturbances. This delayed onset of neurological symptoms, which may begin as minor tremors or mood changes, adds to the diagnostic complexity of the disease. The progression from hepatic to neurological involvement underscores the importance of monitoring patients with Wilson disease for both types of symptoms, as early recognition can significantly improve outcomes (Ferenci et al., 2019).

The diagnosis of Wilson disease remains a clinical challenge due to the diversity of symptoms and the absence of a single definitive test. Laboratory tests such as serum ceruloplasmin levels, urinary copper excretion, and liver function tests are used to assess copper metabolism. A low serum ceruloplasmin level, coupled with elevated urinary copper excretion, is often suggestive of Wilson disease (Ling et al., 2020). Imaging studies, such as brain MRI, may reveal characteristic changes in the basal ganglia, which are indicative of copper deposition. In some cases, liver biopsy may be necessary to directly assess hepatic copper content, providing further confirmation of the diagnosis. Genetic testing for ATP7B mutations has become an essential diagnostic tool, allowing for confirmation of the diagnosis and screening of at-risk family members (Roberts & Walker, 2021). Despite these advancements in diagnostic methods, some patients with atypical or mild symptoms may remain undiagnosed for extended periods, further complicating early intervention (Table 3).

The primary treatment goal in Wilson disease is to reduce copper accumulation and prevent further organ damage. This is typically achieved through lifelong pharmacological therapy. Chelating agents such as penicillamine and trientine are commonly used to enhance copper excretion in the urine, while zinc salts are prescribed to reduce intestinal copper absorption (Socha et al., 2018). In cases of severe liver damage, liver transplantation offers a curative option, as the transplanted liver restores normal copper metabolism. Early diagnosis and initiation of therapy are crucial, as untreated Wilson disease leads to severe morbidity and mortality, particularly due to liver failure or neurological deterioration (Liu et al., 2021).

Wilson disease, though rare, has profound implications for affected individuals and their families. The autosomal recessive inheritance pattern means that siblings of affected individuals have a 25% chance of inheriting the disease, highlighting the need for genetic

counseling and family screening. Advances in genetic testing and molecular diagnostics have improved early detection, even in asymptomatic individuals, enabling early intervention that can prevent or minimize organ damage (Ling et al., 2020). Genetic counseling plays a critical role in managing Wilson disease, as it can help identify carriers and provide a framework for preventive measures, such as early screening in at-risk individuals.

This article aims to enhance understanding of Wilson disease by providing a comprehensive review of its genetic basis, clinical presentation, diagnostic challenges, and treatment strategies. By consolidating current knowledge and emphasizing recent advances in genetic diagnostics and therapeutic options, the article seeks to support clinicians in recognizing the early manifestations of Wilson disease. Ultimately, it highlights the importance of a multidisciplinary approach to improve patient outcomes and reduce the mortality associated with this rare but serious condition. Further research is needed to explore novel therapeutic interventions and address the unmet clinical challenges in managing Wilson disease effectively.

2. Etiology

Wilson disease is a rare autosomal recessive genetic disorder caused by mutations in the ATP7B gene located on chromosome 13. The ATP7B gene encodes a copper-transporting ATPase protein that plays a crucial role in regulating copper homeostasis within the body. This protein is primarily found in the liver and brain and is responsible for the elimination of excess copper via bile. In individuals with Wilson disease, mutations in ATP7B impair the protein's function, preventing the excretion of copper into bile, which leads to toxic copper accumulation in various organs, notably the liver and brain (Liu et al., 2021). As copper builds up in the liver, it spills into the bloodstream and accumulates in other organs such as the kidneys, corneas, and, most importantly, the brain, contributing to the neurological and psychiatric manifestations of the disease (Lutsenko et al., 2019).

3. Epidemiology

Wilson disease is estimated to affect approximately 1 in 30,000 individuals, with a carrier frequency of about 1 in 90 (Ala et al., 2007). The disorder occurs in both males and females equally, although certain populations with a higher rate of consanguinity, such as in certain parts of Asia and the Middle East, may exhibit a higher prevalence (Nagral et al., 2019). While the disease typically manifests between the ages of 4 and 40 years, it can present at any age, with some cases diagnosed in children as young as 3 years old or adults as old as 70 years (Pfeiffenberger et al., 2019).

4. Pathophysiology

At its core, Wilson disease is characterized by defective copper excretion from the liver. Normally, copper is absorbed from the digestive tract and transported into liver cells, where it is incorporated into ceruloplasmin or bound to metallothionein. Excess copper is then transported into the bile for excretion (Lutsenko et al., 2019). In individuals with Wilson disease, the defective ATP7B protein disrupts this copper-transporting process, leading to the retention of copper in the liver. Over time, the excess copper overwhelms the liver's storage capacity, spilling into the bloodstream and being deposited in various organs, most notably the basal ganglia of the brain, the cornea of the eyes, and the kidneys (Gerosa et al., 2019).

In the brain, copper deposition in areas such as the basal ganglia contributes to the movement and psychiatric disorders characteristic of the disease (Takkar et al., 2018). In addition to its role in neurological function, copper is vital for the activity of enzymes such as ceruloplasmin and cytochrome c oxidase, which are involved in antioxidant defense and cellular energy production. The abnormal accumulation of copper leads to oxidative damage within liver cells, contributing to liver dysfunction, chronic hepatitis, cirrhosis, and, in severe cases, liver failure (Lutsenko et al., 2019).

5. Histopathology

In the early stages of Wilson disease, histopathological examination of the liver may reveal moderate fatty infiltration and glycogen deposition within hepatocytes. These changes are often confused with those observed in chronic active hepatitis (Gerosa et al., 2019). While copper levels are elevated in the liver, the early copper deposition is typically confined to the cytoplasm and may not be detectable by conventional histological staining techniques such as rhodamine (Zou et al., 2019). As the disease progresses, copper deposition becomes more widespread, and advanced stages may show signs of cirrhosis and hepatocellular damage.

6. Clinical Presentation and Physical Examination

The clinical presentation of Wilson disease is highly variable, often reflecting the extent of copper accumulation in different organs. Hepatic manifestations are often the first signs of the disease and may include abdominal pain, jaundice, general weakness, and hepatomegaly. Neuropsychiatric symptoms, such as personality changes, depression, tremors, and movement disorders (including chorea and hemiballismus), usually develop later in the course of the disease, often in the second or third decade of life (Hedera, 2019). In some cases, a mask-like facial appearance, dysphonia, spasticity, and muscle rigidity may also be observed (Nazer et al., 1986).

On physical examination, patients may present with hepatosplenomegaly, and in more advanced stages, signs of cirrhosis may be evident. The presence of Kayser-Fleischer (KF) rings, which are copper deposits in the corneal margin, is a hallmark

finding in Wilson disease and can be detected by slit-lamp examination (Capone & Azzam, 2018). However, it is important to note that KF rings can also be seen in primary biliary cirrhosis, which can complicate the diagnosis. Skeletal involvement resembling early-onset osteoarthritis may also be present, particularly in the spine and axial skeleton (Guillaud et al., 2014).

7. Renal and Hematological Manifestations

Renal involvement in Wilson disease may present as Fanconi syndrome, characterized by proximal renal tubular dysfunction, or as urolithiasis, often resulting from copper-induced damage to the renal tubules (Duncan et al., 2016). Hemolytic anemia, occurring in 10-15% of patients, is another common manifestation, resulting from copper-induced oxidative damage to red blood cells (Takkar et al., 2018).

Wilson disease is a complex genetic disorder characterized by impaired copper metabolism, leading to copper accumulation in the liver, brain, and other organs. The diverse clinical presentations, including hepatic, neurological, psychiatric, and renal manifestations, complicate diagnosis and require a comprehensive approach to management. Early diagnosis and intervention are critical to prevent irreversible organ damage, particularly in the liver and brain. Genetic testing, clinical evaluation, and advanced imaging techniques play essential roles in confirming the diagnosis and guiding treatment decisions (Roberts & Walker, 2021). Multidisciplinary management, including the use of chelating agents and liver transplantation in severe cases, remains the cornerstone of therapy, improving long-term outcomes for affected individuals (Poujois et al., 2020).

8. Evaluation of Wilson Disease: Diagnosis and Management

Wilson disease, a rare autosomal recessive disorder caused by defective copper metabolism, requires prompt diagnosis to prevent severe hepatic, neurological, and psychiatric complications. The disorder is primarily due to mutations in the ATP7B gene, which is responsible for copper transport in the liver (Ala et al., 2007). Early detection is crucial, as it can significantly improve outcomes through timely treatment. This paper discusses the diagnostic approach, management, and differential diagnosis of Wilson disease.

8.1 Diagnostic Evaluation

Wilson disease should be suspected in patients exhibiting liver dysfunction, neurological symptoms, or psychiatric abnormalities, particularly when there is a family history of the disease. The diagnostic process begins with clinical suspicion, followed by a combination of laboratory tests and imaging studies.

8.2 Ceruloplasmin Levels: One of the initial diagnostic tests for Wilson disease is measuring serum ceruloplasmin, a copper-carrying protein. In Wilson disease, ceruloplasmin levels are typically reduced to less than 20 mg/dL (normal range: 20–40 mg/dL) (Bandmann et al., 2015). However, ceruloplasmin levels can also be low in other conditions, such as protein deficiencies or inflammatory disorders (Gerosa et al., 2019).

8.3 Urinary Copper Excretion: Elevated copper excretion in the urine is a hallmark of Wilson disease. A 24-hour urine collection showing copper levels greater than 100 mcg/dL is indicative of the disease (Pfeiffenberger et al., 2019). The combination of low ceruloplasmin and elevated urinary copper excretion, especially in the presence of Kayser-Fleischer rings, confirms the diagnosis.

8.4 Kayser-Fleischer Rings: These are copper deposits in the cornea that can be observed using slit-lamp examination. Their presence, along with neurological or psychiatric symptoms, strongly suggests Wilson disease (Takkar et al., 2018). The rings appear as a golden or greenish-brown discoloration at the corneal margin and are considered a diagnostic feature when seen in conjunction with other findings.

8.5 Liver Biopsy: The most definitive test for Wilson disease is a liver biopsy, which allows direct measurement of copper levels in liver tissue. Copper concentrations greater than 250 mcg/g of dry liver tissue confirm the diagnosis (Roberts et al., 2021). Although invasive, liver biopsy is considered the gold standard in the absence of other diagnostic evidence.

8.6 Neuroimaging: In cases with neurological symptoms, magnetic resonance imaging (MRI) is often used. Wilson disease can cause distinctive changes in the brain, particularly in the basal ganglia, which may appear as hyperintensities on T2-weighted MRI images (Zou et al., 2019). In advanced stages, MRI may reveal a characteristic "face of the giant panda" pattern, reflecting brainstem involvement (Ling et al., 2020).

8.7 Additional Laboratory Findings: Liver function tests often show elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in patients with Wilson disease, especially in those with hepatic involvement. In more severe cases, serum albumin levels may decrease due to impaired liver function, and prothrombin time may be prolonged due to a deficiency in clotting factors (Socha et al., 2018). Alkaline phosphatase levels are usually low in patients with acute liver failure related to Wilson disease (Nazer et al., 1986).

8.8 Management and Treatment

The cornerstone of Wilson disease treatment is copper chelation therapy, aimed at reducing copper overload in the body (Table 4). The primary drugs used for this purpose are penicillamine and trientine. Trientine is generally preferred over penicillamine because it has a lower incidence of side effects, particularly nephrotoxicity and rashes (Horn et al., 2019). Both medications work by binding to copper and facilitating its excretion via the kidneys.

In addition to chelation therapy, oral zinc is often prescribed to reduce copper absorption from the gastrointestinal tract. Zinc competes with copper for entry into the enterocyte through the intestinal copper transporter (Roberts et al., 2021). Although zinc supplementation is well tolerated, it is crucial to monitor patients for any gastrointestinal side effects.

9. Liver Cirrhosis and Transjugular Intrahepatic Portosystemic Shunt (TIPS): In cases of liver cirrhosis, patients may develop complications such as variceal bleeding. A TIPS procedure can help manage these complications by shunting blood flow to reduce portal hypertension (Duncan et al., 2016).

9.1 Liver Transplantation: For patients with end-stage liver disease, liver transplantation remains the most effective curative treatment. This procedure can resolve both hepatic and neurological symptoms, as it replaces the defective liver responsible for copper accumulation (Poujois et al., 2020). Liver transplantation is especially beneficial in patients who do not respond to medical therapy (Table 1).

9.2 Neurological Management: Neurological symptoms, such as rigidity, dystonia, and parkinsonism, can be managed with medications like baclofen, levodopa, and anticholinergics such as trihexyphenidyl (Hedera, 2019). In refractory cases, liver transplantation may also improve neurological symptoms (Poujois et al., 2020). Supportive therapies, including physiotherapy and occupational therapy, are essential for managing movement disorders and preventing contractures (Ling et al., 2020).

9.3 Dietary Recommendations: A low-copper diet is recommended for patients with Wilson disease to minimize copper intake. Foods high in copper, such as mushrooms, nuts, shellfish, and liver, should be avoided (Pfeiffenberger et al., 2019).

9.4 Differential Diagnosis

Wilson disease shares symptoms with several other conditions, making diagnosis challenging. It can be mistaken for chronic active hepatitis, other forms of liver disease, or various neuropsychiatric disorders. Parkinsonian syndromes, neuroacanthocytosis, pantothenate kinase-associated neurodegeneration, and Huntington's disease all present with similar neurological features, such as rigidity and movement abnormalities, complicating diagnosis (Członkowska et al., 2018).

Given these overlaps, a thorough evaluation is necessary, including genetic testing, neuroimaging, and liver biopsy when required. Early differentiation is critical for initiating appropriate treatment and preventing irreversible damage (Yüce et al., 2019).

Wilson disease is a complex disorder that requires a multi-faceted diagnostic and therapeutic approach. Early detection, supported by a combination of laboratory tests and imaging studies, is crucial for preventing severe liver and neurological damage. While copper chelation therapy is the cornerstone of treatment, liver transplantation remains the definitive cure for advanced liver disease. A thorough differential diagnosis is essential to distinguish Wilson disease from other conditions with overlapping symptoms. With appropriate management, patients with Wilson disease can achieve favorable outcomes, underscoring the importance of early recognition and intervention.

10. Staging of Wilson Disease

Wilson disease, a genetic disorder caused by defective copper metabolism, progresses through distinct stages. These stages reflect the accumulation of copper in various tissues, with each stage demanding specific treatment interventions to prevent further damage. Understanding these stages is vital for tailoring therapeutic approaches and optimizing outcomes for patients.

Stage 1: Early Copper Accumulation in the Liver

The first stage of Wilson disease is marked by the initial buildup of copper in the liver. Normally, copper is processed in the liver and incorporated into ceruloplasmin, a copper-carrying protein. In Wilson disease, mutations in the ATP7B gene impair this process, leading to copper accumulation in the liver. At this stage, patients may not exhibit noticeable symptoms, but hepatic copper overload is already occurring. Early detection, through monitoring copper levels and genetic testing, is crucial at this phase to initiate treatment before significant liver damage occurs (Ala et al., 2007). Chelation therapy is the primary treatment at this stage to remove excess copper and prevent further hepatic damage.

Stage 2: Redistribution of Copper and Systemic Spread

As Wilson disease progresses, the liver begins to redistribute copper, releasing it into the bloodstream. This copper then circulates throughout the body, depositing in various tissues, most notably the kidneys and the brain. The acute release of copper into the bloodstream often leads to elevated serum copper levels and worsens symptoms, especially in the liver and central nervous system. Clinically, patients may begin to exhibit symptoms such as fatigue, jaundice, and hepatomegaly (Hedera, 2019). Immediate intervention with copper chelators is necessary to reduce copper levels and prevent the progression of copper toxicity to other organs (Horn et al., 2019). Failure to address this stage promptly can lead to irreversible damage to both the liver and neurological systems.

Stage 3: Neurological and Extrahepatic Manifestations

By the third stage, the excess copper accumulated in the liver begins to affect extrahepatic tissues, including the brain. Copper deposits in the basal ganglia and other regions of the brain can cause neurological symptoms such as tremors, rigidity, dystonia, and psychiatric disturbances (Pfeiffenberger et al., 2019). These manifestations significantly impair a patient's quality of life and complicate treatment. Neurological symptoms can sometimes precede liver dysfunction in patients, complicating the diagnosis of Wilson disease. At this stage, more aggressive treatment, such as a

combination of chelation therapy and zinc salts, is essential for reducing the copper burden in the brain and preventing further neurological damage (Bandmann et al., 2015). In some cases, liver transplantation may be required to prevent irreversible hepatic damage.

Stage 4: End-Stage Disease and Organ Failure

The fourth and final stage of Wilson disease is characterized by the development of severe organ damage, often including liver failure and life-threatening neurological impairments. By this stage, the accumulation of copper in both the liver and the brain has led to irreversible damage. Liver failure may manifest as ascites, encephalopathy, variceal bleeding, and portal hypertension (Guillaud et al., 2014). Neurological symptoms can become debilitating, with patients experiencing severe psychiatric disturbances, cognitive decline, and movement disorders. In these cases, liver transplantation becomes a critical therapeutic option. Liver transplantation not only restores liver function but may also alleviate neurological symptoms if performed early enough (Poujois et al., 2020). However, transplantation is not a cure for the neurological effects of the disease, and patients may continue to experience long-term neurological complications.

11. Prognosis of Wilson Disease

The prognosis for individuals with Wilson disease largely depends on the stage at which the disease is diagnosed and treated. Prognostic scoring systems, such as the one developed by Nazer et al. (1986), assess the severity of liver damage by considering factors such as serum AST, bilirubin levels, and prothrombin time. A higher score indicates more severe liver dysfunction and a greater risk of liver failure. Patients with a score of 7 or higher are at high risk of progressing to liver failure and may require liver transplantation. Without treatment, these patients have a life expectancy of just a few weeks. However, with timely intervention and appropriate treatment, including copper chelation and liver transplantation, the prognosis can improve significantly (Guillaud et al., 2014). Following liver transplantation, the survival rate is approximately 87% at 15 years post-transplant (Roberts et al., 2021) (Table 6).

11.1 Complications of Wilson Disease

If left untreated, Wilson disease can lead to a range of serious complications, primarily affecting the liver and nervous system. Hepatic complications include cirrhosis, liver failure, and the development of hepatocellular carcinoma (Gerosa et al., 2019). Neurological complications, such as movement disorders, psychiatric symptoms, and cognitive decline, can also severely affect patients. Additionally, copper accumulation in the kidneys can lead to renal dysfunction and the development of nephrolithiasis (Socha et al., 2018). Early diagnosis and intervention, including the use of copper-chelating agents, are crucial to preventing these complications and improving the long-term prognosis of patients with Wilson disease.

11.2 Postoperative and Rehabilitation Care

Patients who undergo liver transplantation require long-term monitoring to ensure the success of the transplant and the management of Wilson disease. Regular assessments of copper levels, liver function, renal function, and neurological status are essential in the postoperative period. Patients will likely require lifelong chelation therapy to prevent copper buildup in the body, and close monitoring for signs of disease recurrence is necessary. Rehabilitation care, including physical, occupational, and psychiatric support, may also be required to address neurological impairments and improve the patient's quality of life (Członkowska et al., 2018).

11.3 Multidisciplinary Consultations

Managing Wilson disease effectively requires a multidisciplinary approach. Collaboration between specialists in neurology, hepatology, ophthalmology, psychiatry, and genetics is essential to provide comprehensive care for patients. Regular consultations with these specialists help manage the neurological, hepatic, and psychiatric manifestations of the disease and provide the necessary support for patients and their families. Genetic counseling is also an important aspect of care, as it can help prevent the transmission of the disease to future generations (Ling et al., 2020).

Wilson disease is a progressive disorder that can lead to severe liver and neurological complications if left untreated. Early diagnosis, tailored therapeutic interventions, and long-term monitoring are essential for managing the disease and preventing irreversible organ damage. The staging system of Wilson disease helps guide treatment decisions and predict the disease's progression. With timely and appropriate interventions, including copper chelation and liver transplantation, the prognosis for individuals with Wilson disease can be significantly improved.

12. Enhancing Healthcare Team Outcomes in Wilson

12.1 Disease: A Collaborative Approach

Wilson disease (WD) is a rare genetic disorder characterized by the accumulation of copper in various organs, especially the liver and brain (Table 5). Without timely intervention, it can result in severe organ damage, including hepatic failure and neurological impairment. The disease typically manifests during childhood or adolescence, and while copper chelation therapy can control the accumulation of copper, a definitive cure remains elusive. Management of Wilson disease requires a multidisciplinary approach, involving a team of specialists to ensure optimal patient care. This collaborative model is essential due to the complexity of the disease and its systemic effects.

Table 1. Medical Therapies for Wilson Disease

Drug	Mechanism of Action	Route of Administration	Potential Duration of Therapy
British anti-Lewisite or dimercaprol[1]	Copper chelation	Deep intramuscular injection in buttocks	A few weeks or months with drug-free intervals
Penicillamine	Copper chelation	Oral	Lifelong
Trientine	Copper chelation	Oral	Lifelong
Zinc salts	Decreases gastrointestinal copper absorption	Oral	Lifelong
Tetrathiomolybdate[2]	Copper chelation + Decreases gastrointestinal copper absorption	Oral	A few months[2] (see text)

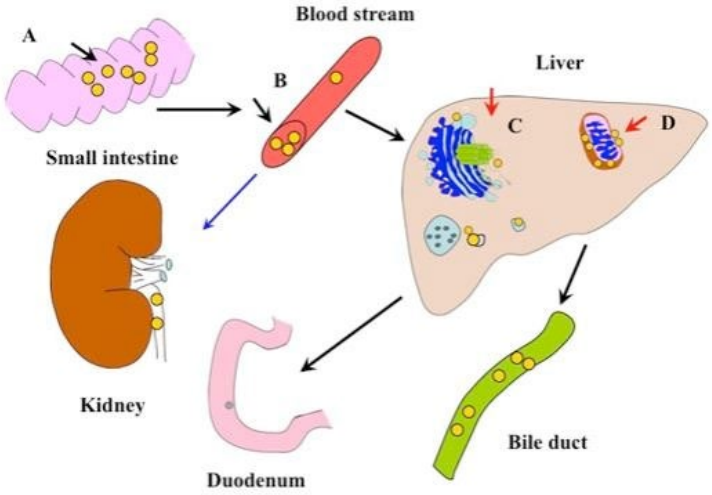

Figure 1. Wilson Disease Review

Table 2. Clinical Features of Wilson's Disease

Clinical Feature	Description	Prevalence (%)
Hepatic Symptoms	Jaundice, hepatomegaly, cirrhosis	60-70%
Neurological Symptoms	Tremors, dysarthria, dystonia, parkinsonism	40-50%
Psychiatric Symptoms	Mood swings, depression, personality changes	30-40%
Renal Symptoms	Fanconi syndrome, nephrolithiasis	10-15%
Ophthalmological Symptoms	Kayser-Fleischer rings, corneal changes	60-70%

Table 3. Diagnostic Methods for Wilson's Disease

Diagnostic Test	Description	Sensitivity (%)	Specificity (%)
Serum Ceruloplasmin Levels	Low levels indicate Wilson's disease	40-60%	95%
24-Hour Urinary Copper Excretion	Increased urinary copper excretion	80-90%	85-90%
Kayser-Fleischer Ring Detection	Seen through slit-lamp eye exam	75-95%	95%
Genetic Testing for ATP7B Mutations	Identifies mutations in ATP7B gene	90-95%	99%
Liver Biopsy (Copper Content Measurement)	Confirmation of copper overload in liver tissue	80-95%	95%

Table 4. Treatment Options for Wilson's Disease

Treatment Option	Mechanism of Action	Indication	Common Drugs/Agents
Chelating Agents	Bind copper to facilitate its excretion	Acute and chronic treatment	Penicillamine, Trientine
Zinc Therapy	Inhibits intestinal copper absorption	Maintenance therapy	Zinc acetate
Liver Transplantation	Replacement of damaged liver in severe cases	End-stage liver disease, acute failure	Orthotopic liver transplant
Ammonium Tetrathiomolybdate	Reduces copper accumulation by blocking its uptake	For refractory cases or acute toxicity	Not widely used, investigational

Table 5. Genetic Insights and Mutations in Wilson's Disease

Gene Mutation	Location	Associated Phenotype	Frequency (%)
ATP7B	Chromosome 13 (13q14)	Primary cause of Wilson's disease	60-70%
ATP7A	X chromosome (Xq13.3)	Menkes disease (copper deficiency)	Rare
COMMD1	Chromosome 18 (18q21.32)	Copper transport defects	Rare

Table 6. Liver Transplantation Outcomes in Wilson's Disease

Study/Year	Transplantation Type	1-Year Survival Rate (%)	5-Year Survival Rate (%)	Recurrence of Wilson's Disease (%)
Guillaud et al. (2014)	Deceased Donor Liver Transplant	94%	85%	5%
Poujois et al. (2020)	Living Donor Liver Transplant	92%	90%	3%
Choudhary et al. (2018)	Living Donor Liver Transplant	95%	90%	0%
Qu et al. (2019)	Domino Cross-auxiliary Transplant	88%	80%	2%

12.2 Multidisciplinary Team Approach

The effective management of Wilson disease relies heavily on an interprofessional healthcare team that includes a gastroenterologist, geneticist, neurologist, mental health nurse, dietitian, nurse practitioner, pathologist, radiologist, and internist. Each of these professionals contributes to addressing different aspects of the disease, which often affects multiple organs, most notably the liver and the nervous system.

12.3 Role of the Gastroenterologist and Geneticist

The gastroenterologist plays a pivotal role in diagnosing and managing the hepatic manifestations of Wilson disease, which may include cirrhosis and liver failure (Ala et al., 2007). In conjunction with the geneticist, the gastroenterologist helps to confirm the diagnosis through genetic testing and clinical assessment. Genetic counseling is essential for preventing the transmission of the defective gene to future generations and provides crucial information for family planning.

12.4 Neurological Management

The neurological aspects of Wilson disease are particularly challenging. Patients may experience cognitive impairment, tremors, dystonia, and ataxia, which significantly impact their quality of life. Neurologists are responsible for diagnosing and managing these symptoms, often utilizing medications such as baclofen and trihexyphenidyl to alleviate spasticity and movement disorders (Bandmann et al., 2015). Regular neurological assessments help monitor the progression of symptoms, allowing for timely adjustments to the treatment plan.

12.5 Role of Dietitians and Mental Health Nurses

Dietitians are integral in managing copper intake through dietary modifications. They help develop personalized meal plans that exclude copper-rich foods like chocolate, nuts, and shellfish (Hedera, 2019). This dietary intervention is crucial in preventing further copper accumulation. Additionally, mental health nurses regularly assess for neuropsychiatric symptoms, which are common in Wilson disease patients. These symptoms may require pharmacological interventions, and mental health nurses play a key role in identifying the need for such treatments early on (Ferenci et al., 2019).

12.6 Nurse Practitioners and Pathologists

Nurse practitioners collaborate with the multidisciplinary team to ensure comprehensive care, often conducting regular assessments and patient education on medication adherence and lifestyle modifications. They also serve as a point of contact for the patient and family, facilitating communication within the team. Pathologists contribute by analyzing diagnostic tests, including liver biopsies and genetic screening, to assess the extent of liver damage and guide treatment strategies (Roberts & Walker, 2021).

12.7 Role of the Pharmacist

Pharmacists are crucial in managing the pharmacological treatment of Wilson disease. Copper chelation therapy, with agents such as penicillamine and trientine, is the primary treatment (Takkar et al., 2018). These medications, while effective in removing excess copper, come with a range of potential side effects, including neurological exacerbations. Pharmacists play a key role in monitoring these side effects and ensuring that the patient adheres to the prescribed regimen. They also educate patients on the importance of avoiding medications that could further damage the liver (Zou et al., 2019).

13. Liver Transplantation and Ongoing Monitoring

Liver transplantation is often the last resort for patients with advanced hepatic Wilson disease. It offers a curative solution for those suffering from end-stage liver disease but presents new challenges, including the need for lifelong immunosuppressive therapy, which can introduce complications (Guillaud et al., 2014). The pharmacist, in collaboration with the transplant team, helps to manage the patient's immunosuppressant medications and monitor for potential adverse effects. While liver transplantation addresses the hepatic manifestations of Wilson disease, it does not resolve the neurological symptoms, which often persist, requiring ongoing treatment (Poujois et al., 2020).

13.1 Physiotherapy and Occupational Therapy

For patients with neurological involvement, physiotherapy and occupational therapy are essential to improving mobility and managing motor symptoms. These therapies help patients with tremors, dystonia, and ataxia by providing exercises and strategies to enhance motor coordination and prevent further physical decline (Członkowska et al., 2018). Occupational therapists also assist patients in adapting to daily tasks, ensuring that they maintain as much independence as possible.

13.2 Nursing Interventions and Patient Education

Nurses are crucial in the holistic management of Wilson disease. They not only provide direct patient care but also ensure that patients adhere to their treatment plans and understand the complexities of their condition. One of the primary nursing interventions is patient education, particularly concerning medication adherence. Nurses educate patients about the importance of lifelong copper chelation therapy and the potential side effects of medications like penicillamine and trientine (Hedera, 2019). They also provide counseling on dietary restrictions and help develop individualized meal plans to prevent copper accumulation. Moreover, nurses monitor patients for neuropsychiatric symptoms, including mood disturbances and cognitive changes, which are common in Wilson disease. Early identification of these symptoms can lead to timely pharmacological interventions. Nurses also work closely with physiotherapists and occupational therapists to manage

the physical symptoms of the disease, providing referrals for therapy when needed (Socha et al., 2018).

13.3 Psychosocial Care

The psychosocial impact of Wilson disease cannot be understated. Patients often experience depression, anxiety, and other neuropsychiatric symptoms due to the chronic nature of the illness and the associated neurological impairments (Ling et al., 2020). Nurses play an essential role in providing emotional support and facilitating access to counseling services. They also work with families to provide coping strategies and ensure that patients have access to a supportive network.

14. Conclusion

Wilson disease is a complex and multifaceted disorder that requires a comprehensive, multidisciplinary approach for effective management. By integrating the expertise of various healthcare professionals, including gastroenterologists, geneticists, neurologists, nurses, dietitians, and pharmacists, patients can receive the care they need to manage both the hepatic and neurological aspects of the disease. The ongoing management of Wilson disease, including copper chelation therapy, liver transplantation, and symptom management, is essential in improving patient outcomes. A collaborative approach ensures that patients receive holistic care, addressing both their physical and psychosocial needs. Through continued education, monitoring, and therapeutic interventions, healthcare teams can significantly enhance the quality of life and long-term prognosis for individuals living with Wilson disease.

Author contributions

R.M.A. conceived and designed the study. T.I.A., A.A.A., H.A.A., S.S.A.A., and A.Y.A.A. contributed to data collection and analysis. K.O.A.A. and B.O.N.A. performed the statistical analyses. M.M.A., T.G.T.A., and H.B.B.A. contributed to the interpretation of the results. A.H.A.A., M.M.M.A., and A.H.M.A. prepared the manuscript draft. H.D.T.A. supervised the study and provided critical revisions to the manuscript. All authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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