Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Review Article
Volume 21 Issue 3- February 2025
DOI: 10.19080/ARGH.2025.21.556064

Adv Res Gastroentero Hepatol

Wilson Disease and the Brain: A Comprehensive Review of Neuropsychiatric Features

Chinyere Pamugo[1], Soura Rajeshwara[2], Angie Gomez Malvacia[3], Eliseo Alberto Quintanilla Cardona[4], Ginelle Cayme[5], Neha Vijay[6], Eric Brodetsky[7], Edgar Josué Sanabria Herrera[8] and Maria Isabel Gomez-Coral[9]*

[1]*UTHealth Science Houston Texas, USA*

[2]*Penn State Milton S. Hershey Medical Center, Hershey, PA, US*

[3]*Universidad Antonio maría Pineda UCLA*

[4]*Universidad de El Salvador, El Salvador*

[5]*University of Texas at El Paso, USA*

[6]*University of Texas at El Paso, USA*

[7]*American University of Antigua St. Johns Antigua*

[8]*Universidad Nacional Autónoma de Honduras*

[9]*Universidad del Valle, México*

Submission: February 06, 2025 **Published:** February 20, 2025

***Corresponding author:** Maria Isabel Gomez-Coral, Universidad del Valle, México

Abstract

Wilson disease (WD) is a rare genetic disorder of copper metabolism caused by mutations in the ATP7B gene, leading to copper accumulation in various organs, including the liver and brain. The neuropsychiatric manifestations of WD are often the first clinical signs and can include mood disturbances, cognitive dysfunction, and motor impairments such as dystonia, tremors, and Parkinsonism. These symptoms frequently mimic primary psychiatric disorders, making early diagnosis challenging. Effective treatment relies on reducing copper overload through chelation therapy with agents like penicillamine or trientine and zinc therapy to inhibit copper absorption. However, even with timely intervention, residual neuropsychiatric symptoms, such as cognitive slowing, mood instability, and executive dysfunction, can persist, requiring ongoing management.

Emerging research aims to improve early detection and personalized treatment strategies for WD by exploring biomarkers like neurofilament light chain (NfL) and cerebrospinal fluid copper levels. Advanced neuroimaging techniques, including diffusion tensor imaging (DTI) and functional MRI, provide insights into WD-related brain changes, even in preclinical cases. Gene therapy and neuroprotective strategies are being investigated to further mitigate neurological damage. Despite advances in treatment, significant unmet needs remain, including the development of standardized guidelines for psychiatric care and long-term studies to assess the impact of different treatments on neuropsychiatric outcomes. Addressing these gaps is crucial to optimizing care and improving the long-term prognosis for individuals with Wilson disease.

Keywords: Wilson disease; Neuropsychiatric manifestations of WD; Copper toxicity

Abbreviations: WD: Wilson Disease; ATP7B: ATPase Copper Transporting Beta Polypeptide; Cu: Copper; ROS: Reactive Oxygen Species; MRI: Magnetic Resonance Imaging; DTI: Diffusion Tensor Imaging; NfL: Neurofilament Light Chain; CSF: Cerebrospinal Fluid; CBT: Cognitive Behavioral Therapy; EKG: Electrocardiogram; NCD: Neurodegenerative Disease; GI: Gastrointestinal; HD: Huntington's Disease; MC: Mitochondrial Copper

Introduction

Wilson's Disease (WD) is a rare genetic disorder of copper metabolism, affecting approximately 1 in 30,000–40,000 individuals worldwide, with a higher prevalence in populations of European descent. However, cases have been reported in Asian and African populations [1]. The disease results from mutations in the ATP7B gene on chromosome 13, which encodes a copper-transporting ATPase responsible for excreting copper into bile and incorporating it into ceruloplasmin. These mutations lead to defective copper transport, causing accumulation primarily in the

liver and subsequently in other organs, including the brain [2]. Copper buildup generates oxidative stress and reactive oxygen species (ROS), leading to mitochondrial damage and cellular dysfunction. This process perpetuates a cycle of further copper accumulation and organ injury, contributing to the progression of WD [1].

The excessive copper deposition in the brain, particularly in the basal ganglia, disrupts movement regulation, leading to neurological symptoms such as parkinsonism, dystonia, and tremors [1-3]. Neurotoxicity also manifests as cognitive decline and psychiatric disturbances, including depression, anxiety, irritability, aggression, and, in some cases, psychosis. These neuropsychiatric symptoms frequently emerge in adolescence or early adulthood and may precede hepatic manifestations, making early diagnosis challenging [1,3]. Due to their overlap with primary psychiatric disorders such as schizophrenia or bipolar disorder, WD is often misdiagnosed, delaying appropriate treatment [3]. While the liver is the first organ affected by copper overload, leading to acute or chronic liver disease, cirrhosis, and even liver cancer, other organs, such as the kidneys and heart, can also suffer damage, resulting in renal dysfunction and cardiomyopathy [4].

Early identification of WD is essential to prevent severe hepatic and neurological complications. However, due to its diverse clinical presentation, diagnosis is often delayed, particularly when neuropsychiatric symptoms mimic primary psychiatric illnesses. A thorough evaluation, including serum ceruloplasmin levels, urinary copper excretion, and liver biopsy, is crucial for accurate diagnosis [1,4]. Treatment primarily focuses on reducing copper accumulation through chelating agents such as penicillamine or trientine and zinc therapy to inhibit intestinal copper absorption. In severe cases, liver transplantation may be necessary. While early treatment significantly improves liver function and alleviates neurological symptoms, some neuropsychiatric manifestations may persist despite copper reduction [1,2,4]. This review aims to provide a comprehensive update on Wilson's Disease, focusing on its epidemiology, pathophysiology, and the impact of neuropsychiatric symptoms on diagnosis and management, to guide healthcare professionals in providing timely and effective treatment.

Pathophysiology of Neuropsychiatric Features in Wilson Disease

Wilson disease (WD) is a genetic disorder of copper [Cu] metabolism originating in the liver [5]. However, excessive Cu deposits or accumulations in various organs, such as the brain, corneas, and liver, malformationally characterize it [6]. Copper primarily accumulates in the brain's basal ganglia, thalamus, cortex, and brainstem, profoundly affecting resting-state networks and contributing to severe neuropsychiatric symptoms such as mood disturbances, cognitive dysfunction, and motor impairments [7]. The basal ganglia, particularly the putamen and globus pallidus, are most commonly affected, causing movement disorders like dystonia and tremors [8]. The underlying pathophysiology of neuropsychiatric features in WD is multifactorial, emanating from Copper accumulation in the liver due to inborn mutations in the Cu(I) transporting ATPase beta polypeptide (ATP7B) [9]. Mutations and inactivation of ATP7B cause Cu overload, disrupting Cu homeostasis and failure of Cu transport in hepatocytes with subsequent impairment of incorporation into the Ceruloplasmin and excretion into the bile and blood [6-10]. The process triggers oxidative stress by promoting the formation of reactive oxygen species (ROS), which damage cellular structures, including lipids, proteins, and DNA [11]. This oxidative damage contributes to neurodegeneration, especially in the basal ganglia, which are highly sensitive to oxidative damage. Hence, copper-induced mitochondrial dysfunction impairs ATP production and further exacerbates cellular injury [12]. Neuroinflammation, mediated by glial activation, also plays a crucial role in neurodegeneration, amplifying the toxic effects of copper buildup in the brain [12]. The altered intra- and inter-network connectivity may explain the neuropathological symptoms and the brain's compensatory response to injury in WD patients [7]. As a result, the combination of copper toxicity, oxidative stress, mitochondrial dysfunction, and neuroinflammation in regions like the basal ganglia results in the progressive neuropsychiatric manifestations seen in Wilson's disease.

Neuropsychiatric Manifestations

In 40-60% of patients, the first clinical manifestations of Wilson's disease are neurological and neuropsychiatric signs [13]. Tremor is often the first specific neurological symptom observed [14]. Other symptoms include dysarthria, dystonia, and choreoathetosis [15]. Some patients also develop cerebellar dysfunction with gait abnormalities [14]. Chorea, tics, myoclonus, and parkinsonism are additional but less common neurological manifestations. Cognitive impairment can occur, particularly involving executive dysfunction, visuospatial processing deficits, memory impairment, and slow processing speed [14]. Autonomic dysfunction is present in around 26-30% of cases, while seizures, hyperreflexia, unusual, stereotyped movements, and tics have been rarely reported [14,15,16]. Behavioral symptoms are a hallmark of Wilson's disease, with common features including personality changes, incongruous behaviour, irritability, and depression [14,15]. As the disease progresses, impulsivity, anxiety, substance abuse, catatonia, and mania may also emerge [15]. Patients with Wilson's disease often develop psychiatric disorders such as bipolar disorder, major depressive disorder, psychosis, schizophrenia, obsessive-compulsive disorder, anorexia, and academic difficulties. Isolated irritability has also been described as a presenting symptom in some cases [17]. Wilson's disease presents a significant neurological-psychiatric overlap, where movement disorders such as tremors, dystonia, and parkinsonism can contribute to neuropsychiatric symptoms. This overlap makes diagnosis challenging, as the symptoms may mimic primary psychiatric illnesses like schizophrenia or affective disorders, further delaying recognition and treatment [15].

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Diagnostic Challenges

The various Wilson's Disease (WD) presentations contribute to diagnostic challenges. Patients can be asymptomatic or exhibit hepatic, neurological, psychiatric, haematological, renal, and ophthalmologic manifestations, or a combination of these [18,19]. Neuropsychiatric symptoms, in particular, include dystonia, dysarthria, drooling, tremors, gait disturbance, dyskinesia, bradykinesia, rigidity, seizures, irritability, disinhibition, apathy, bipolar disorder, anxiety, depression, schizophrenia, and psychosis [20-25]. In children, common symptoms include poor scholastic performance, introversion, choreoathetosis, Parkinsonism, neuroregression, bulbar palsy, catatonia, tremors, and slurred speech [26-29]. Currently, there is no gold standard diagnostic test for WD. Therefore, a combination of clinical assessments and a thorough family history are crucial to establish a definitive diagnosis and exclude other copper metabolism disorders (e.g., Menkes disease, occipital horn syndrome, Indian childhood cirrhosis, MEDNIK syndrome, and Huppke-Brendel syndrome) [30,31].

In addition to the symptoms mentioned above, patients may initially present with joint pain, arthritis, lunulae ceruleae, jaundice, generalized weakness, abdominal pain due to hepatosplenomegaly, and/or hemolytic anemia. Electrocardiogram (EKG) findings may show ventricular hypertrophy, arrhythmias, and nonspecific changes in T waves and ST segments. Kayser-Fleischer rings on slit-lamp examination can also help narrow the differential diagnosis. A methodical diagnostic approach using the Leipzig score is available. Developed in 2001, this scoring system incorporates clinical findings and results from serum ceruloplasmin, urine copper, ATP7B mutations, and liver biopsy assessments. A score of 4 or greater indicates a probable WD diagnosis [32-34]. The radioactive copper test has also been reported to aid diagnosis [35]. MRI findings in WD can include hyperintense and mixed-intensity changes in the putamen and globus pallidus. Midbrain involvement is evidenced by the classic "giant panda" sign, characterized by bilateral hyperintensities in the substantia nigra and red nucleus [36,37]. A "double panda" sign has also been reported in more advanced stages of WD [38,39]. A recent correlational study has found that damage to the putamen, pons, and thalamus is a common neuroimaging finding in patients with dystonia. Additionally, choreoathetosis has been linked to damage in the caudate nucleus [40].

Management of Neuropsychiatric Features

Due to the complex presentation of Wilson's Disease (WD), it should only follow that the appropriately sought-after care spans across multiple specialties. While WD is primarily recognized as a hepatic disease, particularly in younger cohorts, due to the early accumulation of copper recognized in childhood, the neuropsychiatric components inherit the importance of including neurologists and psychiatrists in prospective workup and medical management [41]. Recognizing a classical neurological symptom, such as dystonia, can indicate several neurological conditions and broaden the number of differential diagnoses in a potential WD patient to include other diseases with similar presentations, such as Parkinson's [41]. However, the involvement of hepatologists in conducting liver function tests or biopsies as supportive evidence to discern hepatological manifestations such as cirrhosis, liver failure, or hepatosplenomegaly, can be beneficial in ruling out parkinsonian symptomology versus hepatolenticular degeneration, as well as in determining treatment plans across age stratifications [42].

Chelation therapy in patients with WD has been initially suggested as a favourable pharmacological treatment method, given its ability to reverse mitochondrial damage brought on by oxidative stress secondary to free copper accumulation in the blood [42,43]. D-penicillamine is a chelating agent that Favors the urinary excretion of copper in addition to faecal elimination by mobilizing free copper in the body [43]. Although D-penicillamine is a cost-effective drug that provides considerable symptomatic treatment, it can come with adverse effects contributing to nephrotoxicity, dermatological abnormalities, as well as initial neurological worsening, leading some to opt for other treatment options such as trientine or zinc salts [44]. Trientine, also favouring urinary excretion of copper via chelation, is a therapy option available to those intolerants to Penicillamine and has enhanced effects when used in conjunction with zinc, which blocks intestinal absorption of copper and increases faecal copper excretion [45].

Zinc therapy has since gained traction as a recommended method of therapy through its ability to remove excess copper from the blood without inducing adverse neurological symptoms, as studied in the use of D-penicillamine or trientine, making it a preferred choice for maintenance therapy [46]. Symptomatic treatment for patients with WD presenting with symptoms such as dystonia or tremors also contributes toward a significant portion of multidisciplinary management. Data remains limited due to the nature of retroactive analyses; however, recent studies have shown that anticholinergics, botulinum toxin, baclofen, and beta blockers positively affect neurological symptomatic management [47]. While there are challenges present, whether with the adverse reactions of pharmacological treatments or with patient compliance with treatment in younger populations due to earlier presentation of etiologist, it remains crucial for WD patients to continue receiving treatment in conjunction with symptomatic management, as treatment cessation has been shown to trend with a high mortality rate [43].

In addition to pharmacological management, treatments including cognitive therapy, physiotherapy, and even dietary changes to restrict high copper-containing foods, or 'lifelong decoppering,' have been suggested for further management of the neuropsychiatric features of WD [42,49]. Cognitive therapy, intervening at multiple levels, including affective, cognitive,

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behavioural, and psychophysiological, has improved cognitive processing and emotional management. Cognitive behavioural therapy (CBT) with an emphasis on relaxation therapy was shown to improve symptoms secondary to depression and anxiety, which, in turn, showed improvement in the frequency of muscle contractions, which are commonly seen in neuromuscular presentations of WD [50].

Prognosis and Outcomes

The prognosis of neuropsychiatric symptoms in Wilson disease (WD) is highly dependent on the timing of diagnosis and the initiation of treatment. Early diagnosis and timely intervention significantly improve neurological and psychiatric outcomes by preventing irreversible damage caused by copper accumulation in the brain. Patients who begin chelation or zinc therapy in the early stages of the disease often experience substantial symptom improvement, with some achieving near-complete resolution of neuropsychiatric deficits. In contrast, late diagnosis, particularly in individuals presenting with severe neuropsychiatric or motor symptoms, is associated with poorer outcomes. Advanced neurological impairment, cognitive decline, and persistent psychiatric disturbances may not fully reverse despite effective copper chelation, highlighting the critical importance of early recognition and treatment initiation [51-53].

Long-term management of neuropsychiatric symptoms in WD requires a multidisciplinary approach involving hepatologists, neurologists, psychiatrists, and rehabilitation specialists. Regular monitoring of copper levels, adherence to chelation therapy, and comprehensive psychiatric care are essential to preventing disease progression. Even in patients with effective treatment, residual neuropsychiatric symptoms such as cognitive slowing, mood instability, and executive dysfunction can persist, necessitating ongoing psychiatric and cognitive rehabilitation interventions. Addressing these residual symptoms with targeted pharmacologic and non-pharmacologic strategies can enhance the quality of life and functional outcomes [51-54].

The prognosis in WD is also influenced by several factors, including the severity of neurological involvement at diagnosis, the patient's adherence to treatment, and individual variations in response to chelation therapy. Some patients experience paradoxical neurological worsening when initiating chelation therapy, a phenomenon thought to be due to rapid mobilization of copper from brain tissues, emphasizing the need for careful treatment adjustments. Additionally, genetic heterogeneity in ATP7B mutations may contribute to disease progression and treatment response variability [51-53]. Future research into prognostic biomarkers may help refine risk stratification and guide more personalized therapeutic approaches to optimize long-term neuropsychiatric outcomes.

Future Directions

Emerging research into the neuropsychiatric manifestations of Wilson disease (WD) is focused on identifying biomarkers that could enable earlier and more precise detection of brain involvement. Potential biomarkers, such as neurofilament light chain (NfL) and cerebrospinal fluid (CSF) copper levels, are being explored for their diagnostic and prognostic value in monitoring disease activity and treatment response [55-57]. Advances in genetic analysis, including whole-genome sequencing, offer the possibility of refining diagnostic criteria and predicting individual susceptibility to neurological and psychiatric symptoms, which could lead to more timely therapeutic interventions [55].

In addition to biomarker research, advanced imaging techniques like diffusion tensor imaging (DTI) and functional MRI provide valuable insights into brain changes associated with WD, even in preclinical cases [56]. These modalities have revealed alterations in white matter integrity, basal ganglia connectivity, and cortical dysfunction, suggesting that neuroimaging could be a powerful tool for early detection, monitoring treatment efficacy, and distinguishing WD-related symptoms from other disorders [56]. Furthermore, novel therapeutic approaches, such as gene therapy to restore ATP7B function and neuroprotective strategies to mitigate neuronal damage, are being explored [54-57]. Despite progress, there remain significant unmet needs in WD management, including standardized guidelines for psychiatric care, long-term studies on treatment impact, and targeted interventions for cognitive and psychiatric rehabilitation.

Conclusion

Wilson disease (WD) presents significant challenges in both diagnosis and management, particularly regarding its neuropsychiatric manifestations. Early identification and timely intervention are crucial in preventing irreversible brain damage and improving both neurological and psychiatric outcomes. Although current treatments, such as chelation therapy and zinc supplementation, have been effective in managing copper overload and alleviating symptoms, residual neuropsychiatric disturbances often persist, underscoring the need for continued psychiatric and cognitive rehabilitation. Moreover, the overlapping nature of neurological and psychiatric symptoms makes WD a complex condition to diagnose, often resulting in delays that hinder optimal treatment outcomes. Advances in biomarker discovery, genetic analysis, and neuroimaging hold promise for enhancing early detection and personalized therapeutic approaches, improving the long-term prognosis of patients with WD. While progress has been made in treatment strategies, there remains an urgent need for standardized guidelines for psychiatric care, long-term monitoring of treatment effects, and targeted interventions for cognitive and psychiatric rehabilitation. Addressing these gaps

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is essential to ensure improved patient care, reduce disease progression, and enhance the overall quality of life for individuals with Wilson disease.

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