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Review Article

Diagnostic challenges and mimicking disorders of Wilson's Disease: A comprehensive review

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Abstract

Wilson disease is classically defined as an autosomal recessive disorder of copper metabolism that leads to neurological and hepatic dysfunction. It is one of the most prevalent genetic liver disorders caused by pathogenic mutations in the *ATP7B* gene, leading to defective copper transport and toxic accumulation in tissues. Without timely diagnosis and appropriate treatment, Wilson disease can progress to life-threatening hepatic failure and severe neurological impairment, ultimately resulting in death. Clinically, Wilson disease exhibits marked phenotypic heterogeneity, presenting with a wide spectrum of hepatic, neurological, and psychiatric symptoms. Differential diagnosis can be complicated by other inherited metabolic disorders with overlapping clinical and biochemical features, collectively referred to as Wilson's mimicry disease. These disorders may contribute to diagnostic uncertainty, potentially delaying the identification of Wilson disease and timely initiation of effective therapy. In this review, we collated pertinent information on Wilson disease and its related differential diagnoses based on a broad review of the scientific literature. Our findings highlight disorders that closely mimic Wilson disease clinically and biochemically, outlining their distinguishing clinical, biochemical, and genetic features, which can be differentiated through specific diagnostic markers and genetic testing. Enhancing awareness and understanding of these entities is essential to improve diagnostic accuracy in pediatric neurology and hepatology.

Keywords: Wilson Disease (WD), *ATP7B*, Copper metabolism, Differential diagnosis.

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Anthracosis Copper is an essential trace element required in minute amounts to maintain optimal health, predominantly stored in the liver, with lesser concentrations in the brain, heart, kidneys, and skeletal muscles (1). It plays a critical role in the function of key enzymes, facilitating the synthesis of hemoglobin, myelin, and melanin, while also supporting thyroid gland function. Furthermore, copper contributes to the structural integrity of skin, epithelium, blood vessels, and connective tissues by enabling collagen and elastin cross-linking (2). Imbalanced copper homeostasis, whether through deficiency or excess, can adversely impact human development, underscoring the critical need for tightly regulated homeostatic mechanisms (3). Wilson disease (WD) is a rare autosomal recessive disorder caused by mutations in the *ATP7B* gene on chromosome 13q14.3, leading to pathological copper accumulation in the liver, brain, and other organs. The *ATP7B* gene encodes a copper-transporting P-type transmembrane ATPase, primarily expressed in the liver, which regulates copper homeostasis by transferring copper to the trans-Golgi network of hepatocytes and incorporating it into ceruloplasmin, a key copper-binding protein released into the bloodstream (4). Ceruloplasmin plays a critical role in copper transport and metabolism, binding approximately 95% of circulating copper in the blood (5).

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Within hepatocytes, ceruloplasmin facilitates the incorporation of copper into apoceruloplasmin to form functional holoceruloplasmin, which is essential for stable copper transport and preventing cellular toxicity (5). ATP7B also facilitates the excretion of excess copper into bile. Figure 1 depicts normal copper metabolism and homeostasis in the presence of functional ATP7B. In WD, defective ATP7B impairs ceruloplasmin's ability to bind copper, leading to reduced serum ceruloplasmin levels and increased toxic free copper accumulation in hepatocytes, which causes mitochondrial damage, periportal inflammation, hepatocyte injury, fibrosis, and ultimately liver cirrhosis (6, 7). Additionally, stored copper is released into the bloodstream, where it accumulates in other organs (e.g., brain, cornea, kidney), causing further symptoms due to the high toxicity of free copper to most tissues. Figure 2 illustrates impaired copper metabolism resulting from mutated ATP7B in WD (8).

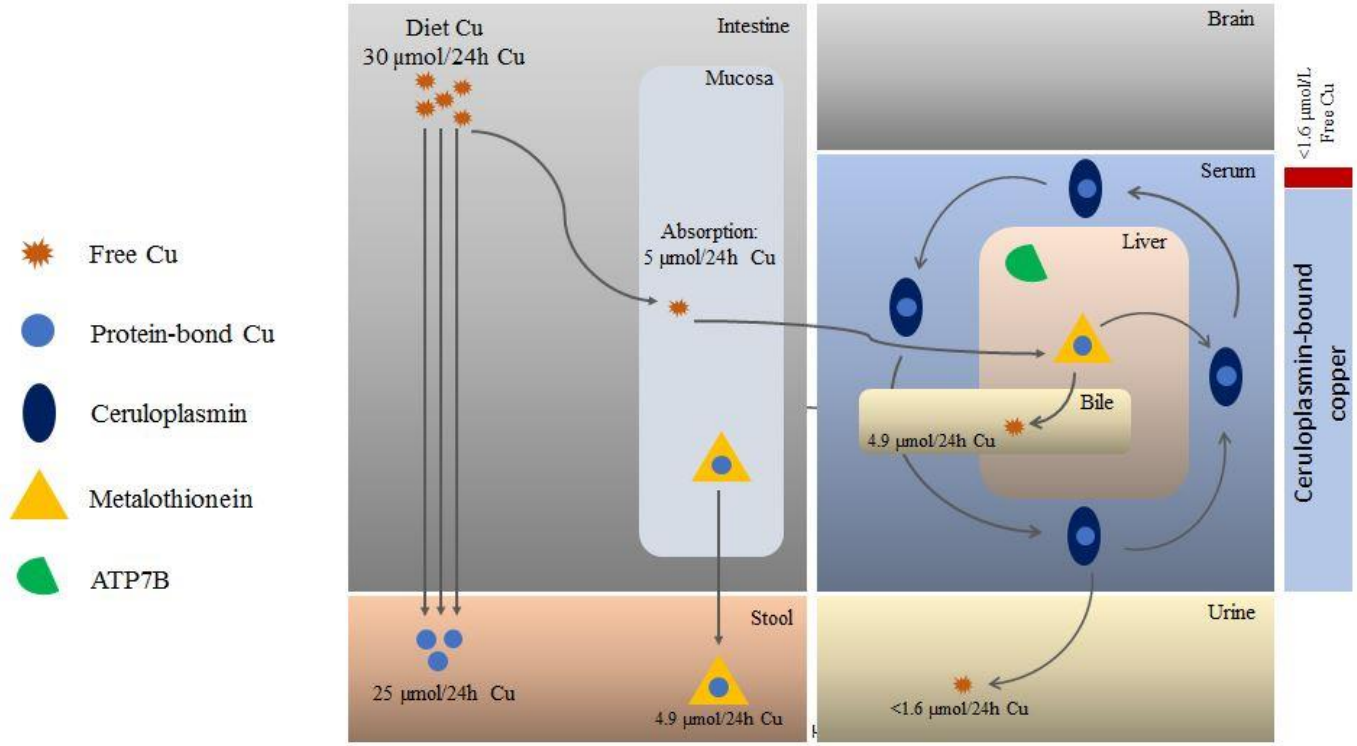

Figure 1. The diagram above represents regular copper metabolism and a healthy copper (Cu) balance. In this scenario, the daily intake of copper from the diet is approximately 30 µmol or 2 mg per 24 hours. The combined excretion of copper through feces and urine amounts to about 25–30 µmol, equivalent to 1.5–2 mg per 24 hours. Around 85–95% of the total serum copper is firmly bound to ceruloplasmin. At the same time, the remainder exists in an unbound or loosely bound (free) form.

The prevalence of WD is estimated to be between 1 in 30,000 and 1 in 100,000 individuals worldwide (9). Since the disease is inherited in an autosomal recessive manner, its incidence may increase due to founder effects and consanguineous marriages. Therapeutic options for WD currently include chelating agents such as D-penicillamine, trientine, and zinc supplements, as well as liver transplantation. Additionally, a diet low in copper content can be beneficial (10, 11).

Clinical features

WD is a clinically heterogeneous disorder characterized by a wide spectrum of manifestations, primarily including hepatic, neurological, and psychiatric presentations. Early in life, patients are typically asymptomatic; however, gradual copper accumulation leads to variable subclinical liver disease (12). Symptoms in such cases may include abdominal pain, hepatosplenomegaly, jaundice, and loss of appetite. Patients presenting primarily with hepatic manifestations tend to be younger than those with predominantly neurological symptoms. Overall, it is estimated that hepatic symptoms occur approximately 10 years earlier than neurological symptoms (13). The age at onset (AAO) of liver symptoms in children with WD averages around 10 years, while neurological

manifestations typically appear between 15 and 21 years of age, although some patients may exhibit neurological symptoms before age 10 (14). Neurological manifestations are generally associated with a significantly longer interval from symptom onset to diagnosis compared to hepatic manifestations (15). Common neurological signs of WD include dysarthria, dystonia, tremor, Parkinsonism, dysphagia, ataxia, bradykinesia, and other extrapyramidal symptoms, with gait abnormalities seen in 44–75% of individuals (16). Less common neurological symptoms include epilepsy and neuropathy (17). The psychological aspects of WD can appear before or during disease progression and include anxiety, depression, psychosis, autonomic disturbances, apathy, sleep disorders, and cognitive abnormalities (18, 19). Copper accumulation may also lead to cardiomyopathy, arthropathy, hypoparathyroidism, and kidney damage (20, 21). WD can manifest at any age from early childhood to the sixth decade, though it generally occurs in children and young adults, with a peak incidence around 17 years (16). The youngest diagnosed case was a 9-month-old with hepatic manifestations (22). Results from a large study show that about 8% of patients exhibit clinical signs of WD after age 35, and about 4% after age 40 (23).

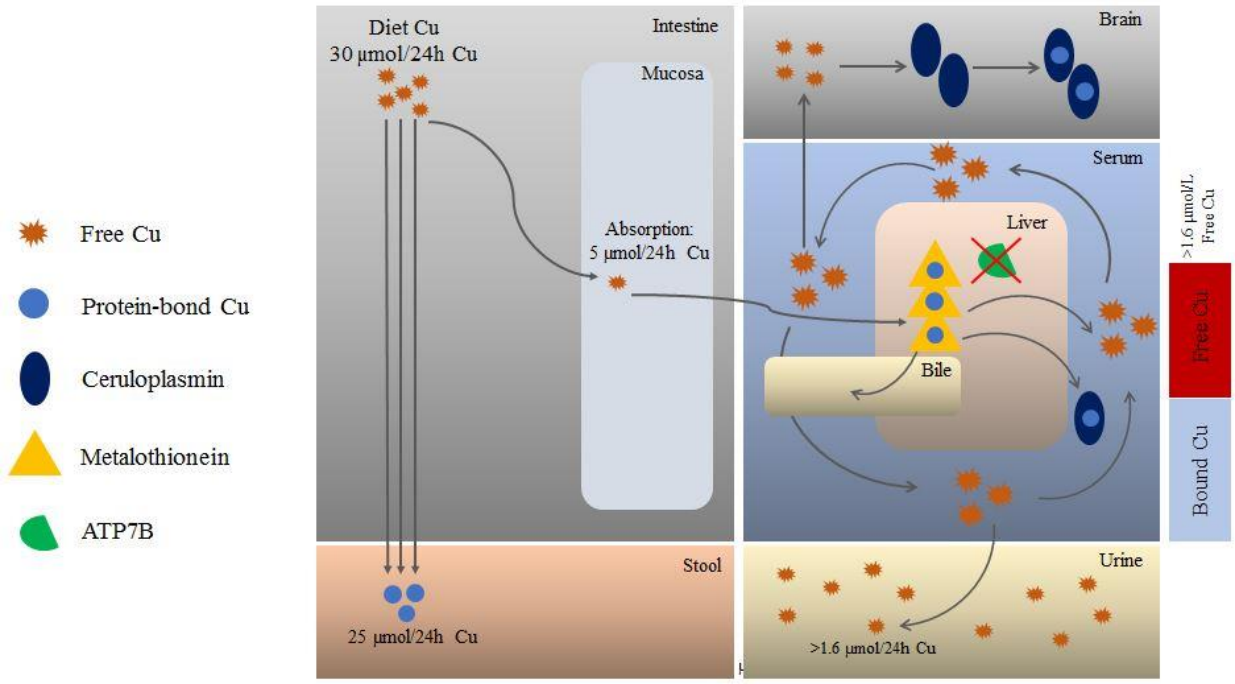

Figure 2. In WD, there is a disruption in copper metabolism, leading to reduced synthesis of holoceruloplasmin and diminished excretion of free copper in bile. Without treatment, the total excretion of copper via urine and stools remains slightly lower than usual, which increases the risk of copper toxicity. Serum-free copper can either be bound by metallothioneins, deposited in organs (especially the liver), or excreted in the urine.

The rate of disease progression varies due to factors such as environmental and genetic modulators, including epigenetic factors, sex, and modifier genes. The variability in clinical manifestations and AAO among patients with the same *ATP7B* gene mutation underscores the importance of these factors (24). However, the penetrance of different *ATP7B* mutations greatly influences phenotypic severity. Figure 2 illustrates impaired copper metabolism in WD, wherein the production of holoceruloplasmin and the excretion of free copper via bile are reduced.

Diagnostic methods for WD

Urinary copper excretion

Urinary copper excretion is a key diagnostic marker for WD. The 24-hour urinary copper level, typically ranging from 0.64–1.60 µmol/24 h, provides moderate sensitivity (50–80%) and high specificity (75.6–98.3%) for WD diagnosis, with accuracy dependent on proper sample collection and laboratory quality (25). In early-stage or asymptomatic patients, levels may fall below diagnostic thresholds. The penicillamine challenge, using 500-mg doses over 24 hours, enhances diagnostic accuracy, particularly in symptomatic patients. Spot urine copper or copper-to-creatinine ratio is less reliable for definitive diagnosis (26).

Ceruloplasmin of serum

Ceruloplasmin is the primary copper-carrying protein in plasma. Its serum levels vary with age and are considered more reliable for diagnosis in children over one year of age. As an acute-phase reactant, ceruloplasmin levels may increase during inflammation or decrease in liver disease and malnutrition, complicating interpretation. In WD, levels are typically low but may appear normal during infections (27). Enzymatic assays measure the active, copper-bound form, whereas immunologic methods detect both active and inactive forms (28). A serum level below 0.2 g/L supports a diagnosis of WD; however, up to 20% of affected patients may present with normal levels, necessitating further diagnostic evaluation (29).

Serum copper levels

In WD, serum copper is often low due to poor binding to apo-ceruloplasmin, but may appear normal or elevated in acute liver failure or hemolysis (27). Non-ceruloplasmin-bound copper exceeds 200 µg/L in WD, compared to 50–100 µg/L in healthy individuals. Exchangeable copper (CuEXC) measures free copper, with levels >2.08 µmol/L indicating overload. Relative exchangeable copper (REC) >18.5% offers 100% sensitivity and specificity for WD diagnosis (30-32).

Copper accumulation in the liver

Liver biopsy remains the definitive diagnostic tool when non-invasive methods are inconclusive or differential diagnoses are considered. A hepatic copper level above 250 µg/g dry weight is diagnostic, though sampling variability and secondary copper accumulation in other liver disorders require multiple specimens for accuracy (33).

Magnetic Resonance Imaging in Wilson's Disease

MRI in hepatic studies

MRI plays a role in evaluating liver lesions in WD by assessing nodule intensity and size, which contribute to cirrhosis classification. While variations in signal intensity may serve as diagnostic biomarkers, overlapping features from conditions like alcohol-related liver disease can hinder specificity (34).

MRI in neurological studies

Brain MRI in most patients with neurological manifestations reveals characteristic findings, including T2 hyperintensities in the basal ganglia, white matter, and thalami, as well as brain atrophy and T2 hypointensities in the basal ganglia (35). Additionally, classic imaging signs such as the "face of the giant panda" in the midbrain and, in some cases, the "face of the miniature panda" in the pontine tegmentum may be observed (36). Evaluation of the KF ring can be performed using Optical Coherence Tomography (OCT), offering enhanced sensitivity in detecting early corneal copper deposits (37).

Deep learning and genetic analysis

CNN models are used to analyze liver images for WD by processing dense lesion data. These models perform convolution and pooling to extract relevant features. The integration of genetic profiling, chromatin shift, and genomic biomarkers with CNN has improved WD diagnosis. Additionally, recurrent neural networks (RNNs) and long short-term memory (LSTM) networks have been applied to genetic data to aid in classification, offering insights into molecular patterns (38, 39).

Genetic mutation analysis

Genetic testing of the *ATP7B* gene confirms diagnosis in over 95% of cases, often identifying two causative alleles. However, incomplete detection or access limitations may yield only one or no identifiable variant. In such cases, diagnosis depends on clinical and biochemical findings. New techniques, such as Next Generation Sequencing (NGS), enhance mutation detection, especially for variants outside coding regions, large deletions or duplications. If a mutation is detected, Screening of first-degree relatives and genetic counseling are strongly recommended (40, 41).

Similar metal-related metabolic disorders to WD

Several disorders can mimic WD and phenotypically overlap with it, complicating accurate clinical diagnosis. This review describes inherited metabolic disorders with manifestations similar to WD, which should be considered for accurate differential diagnosis. We also discuss treatment strategies, diagnostic challenges, and how each disorder differs from WD. A small number of rare metal-related metabolic disorders present symptoms similar to WD (table 1). These disorders, primarily affecting the liver and brain, mimic WD diagnostic features such as decreased serum copper and ceruloplasmin levels, increased liver copper, and increased 24-hour urinary copper excretion. Additionally, some environmental liver diseases may lead to the misdiagnosis of WD. For a comparative summary of the clinical and biochemical features of these metal-related metabolic disorders resembling WD, refer to table 1.

MEDNIK syndrome

MEDNIK syndrome, an ultra-rare autosomal recessive disorder of copper metabolism, results from mutations in the AP1S1 gene, encoding a subunit of the adaptor protein (AP) complex 1, which is essential for intracellular trafficking of ATP7A (Menkes) and ATP7B (Wilson) proteins (43). This multisystem condition manifests with overlapping features of Wilson's and Menkes diseases, including liver copper accumulation, hepatopathy, low

serum ceruloplasmin and copper levels, increased 24-hour urinary copper excretion, and brain MRI findings like basal ganglia T2 hyperintensity. Distinctive traits include neurocutaneous manifestations such as severe mental retardation, deafness, enteropathy, ichthyosis, keratoderma, and dysmorphic features (high forehead, low-set ears, low nasal bridge). Neurological symptoms typically emerge earlier than in WD. (52). Elevated levels of very-long-chain fatty acids (VLCFA) in plasma serve as another diagnostic marker for MEDNIK syndrome (53). Zinc acetate treatment has been notably successful in improving clinical conditions and reducing liver copper overload (54).

Hypermanganesemia with dystonia 1

Hypermanganesemia with dystonia 1 (HMNDYT1), a rare autosomal recessive disorder, closely mimics WD. It arises from mutations in the *SLC30A10* gene, which encodes a manganese transporter, leading to defective manganese excretion and its accumulation in the liver and brain, without changes in urinary copper excretion (55, 56). Clinical manifestations include early-onset dystonia, polycythemia, iron depletion markers, and distinctive brain MRI findings (T1-hyperintensity in basal ganglia and white matter, with pathognomonic sparing of the ventral pons). Liver involvement ranges from hepatomegaly, elevated transaminases, and unconjugated hyperbilirubinemia to severe outcomes like cirrhosis or liver failure (57). Neurological symptoms, such as dystonia, dysarthria, spasticity, gait disturbances, bradykinesia, and parkinsonism, typically present in childhood (1st-2nd decade) or adulthood (5th-6th decade). (45, 57). Treatment involves chelating agents, such as disodium calcium edetate or D-penicillamine, combined with oral iron supplementation to address manganese overload and mitigate clinical symptoms (58).

Table 1. Overview of general diagnostic features for inherited metabolic disorders similar to Wilson disease

	Wilson disease	MEDNIK syndrome	HMNDYT 1	HMNDYT 2	HBS	ACP	NP-C	CDGs	MDR3 Deficiency	Menkes disease
Causative gene	*ATP7B*	*AP1S1*	*SLC30A10*	*SLC39A14*	*SLC33A1*	*CP*	*NPC1/NPC2*	Multiple gene	*ABCB4*	*ATP7A*
Inheritance	AR	AR	AR	AR	AR	AR	AR	Variable, Mostly AR	AR	XLR
Pathogenesis (related to metals)	Copper overload	Copper overload	Manganese overload	Manganese overload	-	Iron overload	Effect on copper homeostasis	Copper overload	Copper overload	Copper deficiency
Age of onset	Mostly Childhood or young adults	Mostly Childhood	Childhood or adult-onset	Early childhood	Infancy/early childhood	Late adulthood	Late-infancy to early adulthood	Infancy to childhood	Variable, Neonatal to adulthood	Infancy to adolescence
Hepatic impairment	+	+	+	-	-	+	+/-	+/-	+	+
Neurological impairment	+	+	+	+	+	+	+	+/-	-	+

	Wilson disease	MEDNIK syndrome	HMNDYT 1	HMNDYT 2	HBS	ACP	NP-C	CDGs	MDR3 Deficiency	Menkes disease
Psychiatric impairment	+	+/-	+	+	NA	+	+	+/-	-	NA
Basal ganglia abnormalities	+	+	+	+	-	+	+	+/-	-	+/-
KF Rings	+	-	-	-	-	-	-	-	-	-
Serum copper	D	D	NA	NA	D	D	D	D	D	D
Serum ceruloplasmin	D	D	NA	NA	D	D	D	D	D	D
SGPT/SGOT	I	I	I	I	-	I	I	I	I	-
Liver copper deposition	I	I	NA	-	-	I	Normal or I	I	I	-
Urinary copper excretion	I	I	Normal	Normal	Normal	Normal	Normal or D	I	I	-
References	(42)	(43)	(44)	(45)	(46)	(47)	(48)	(49)	(50)	(51)

HMNDYT, Hypermanganesemia with dystonia; HBS, Huppke-Brendel syndrome; ACP, Aceruloplasminemia; NP-C, Niemann–Pick type C; MDR3, Multidrug resistance protein 3; CDG, Congenital disorders of glycosylation; AR, Autosomal Recessive; XLR, X-linked Autosomal Recessive; +, Present; -, Absent; D, Decreased; I, Increased; NA, Not Available

Hypermanganesemia with dystonia 2

Hypermanganesemia with dystonia 2 (HMNDYT2), caused by biallelic *SLC39A14* gene mutations encoding the manganese transporter SLC39A14, presents with early childhood Parkinsonism/dystonia due to brain manganese overload. Unlike HMNDYT1, it lacks polycythemia, liver manganese accumulation, or liver disease (45, 59).

Treatment includes manganese chelation, anti-spasticity drugs, L-dopa, and dietary manganese restriction (45).

Huppke-Brendel syndrome (HBS)

Huppke-Brendel syndrome (HBS), an ultra-rare autosomal recessive disorder of copper metabolism, is caused by *SLC33A1* gene mutations encoding an acetyl CoA transporter on the ER membrane. It presents with congenital cataracts, sensorineural hearing loss, developmental delay, brain MRI hypomyelination, cerebellar hypoplasia, hypotonia, and motor impairment in infancy, with death occurring between 10 months and 6 years (60, 61). Unlike WD, HBS lacks copper overload or hepatic cirrhosis but shows low serum copper and ceruloplasmin levels. Impaired acetylation of ceruloplasmin and other proteins underlies the disease (62).

Aceruloplasminemia (ACP)

Aceruloplasminemia (ACP), an autosomal recessive neurodegenerative disorder caused by *CP* gene mutations encoding ceruloplasmin, is classified as a neurodegeneration with brain iron accumulation (NBIA) phenotype. It features iron accumulation in the liver and brain, particularly the basal ganglia, cerebellum, thalamus, and cortex, complicating differentiation from WD (63). Unlike WD, ACP involves iron overload, with low serum copper and iron, high ferritin, and very low or undetectable ceruloplasmin levels (55). Neurological symptoms, presenting in late adulthood (50–60 years), include cerebellar ataxia, dysarthria, dystonia, chorea, tremor, Parkinsonism, and cognitive impairment, alongside diabetes mellitus, anemia, and retinal degeneration. Severe cases may involve liver copper accumulation and life-threatening heart failure. (2, 64). Some heterozygous individuals show symptoms like ataxia (65). Iron chelation reduces serum ferritin and liver iron but has uncertain efficacy against neurodegeneration (66).

Niemann–Pick type C (NP-C)

Niemann–Pick type C (NP-C), a rare autosomal recessive lysosomal storage disorder, results from biallelic mutations in NPC1 (95%) or NPC2 (5%) genes, causing defective cholesterol and lipid trafficking with lysosomal accumulation in organs, including the brain. Classic NP-C manifests in late infancy with hypotonia and developmental delay, progressing to ataxia, dysarthria, dysphagia, dystonia, psychiatric issues, dementia, seizures, and gelastic cataplexy (67). Brain MRI reveals atrophy, white matter changes, and basal ganglia alterations (48). Liver complications include neonatal cholestatic jaundice, hepatosplenomegaly, and severe liver failure in ~10% of cases (68). Disrupted copper homeostasis, with low serum copper and ceruloplasmin, resembles WD, risking misdiagnosis (69, 70). Therefore, NP-C is a key differential diagnosis for WD. No specific approved treatment exists.

Congenital disorders of glycosylation (CDGs)

Congenital disorders of glycosylation (CDGs), a diverse group of metabolic disorders caused by defective protein glycosylation, include subtypes like TMEM199-CDG, PMM2-CDG, CCDC115-CDG, COG2-CDG, ATP6AP1-CDG, and PGM1-CDG, which mimic WD (55). PGM1-CDG, due to phosphoglucomutase 1 defects (PGM1 gene), shows low serum copper, low ceruloplasmin, and elevated liver copper, resembling WD. Diagnosis relies on transferrin isoelectric focusing and high-resolution mass spectrometry (71). Hepatic involvement may lead to WD misdiagnosis. Distinct features include neurological symptoms, brain MRI abnormalities (developmental defects), and symptoms like cleft uvula, dilated cardiomyopathy, rhabdomyolysis, and hypoglycemia (71, 72). It is crucial to avoid treating these Wilson-like CDG subtypes with oral chelating agents or zinc supplements, as such treatment is generally unnecessary. Dietary galactose supplementation may improve PGM1-CDG outcomes (73).

Multidrug resistance protein 3 (MDR3) deficiency

Multidrug resistance protein 3 (MDR3) deficiency, a rare inherited cholestatic disorder caused by ABCB4 gene mutations, is classified as progressive familial intrahepatic cholestasis type 3 (PFIC3). MDR3, a hepatocanalicular floppase, transports biliary phospholipids (phosphatidylcholine). Its defects reduce bile phospholipids, producing hydrophilic bile that impairs bile salt inactivation, leading to biliary epithelium injury, increased lithogenicity, chronic cholestasis, and cirrhosis (74, 75). Phenotypes range from infantile hyperbilirubinemia and cholestasis to young adult cirrhosis. Some cases mimic WD with abnormal urinary copper excretion, low serum ceruloplasmin, and elevated liver copper, necessitating molecular diagnostics to differentiate from WD (55). This highlights the importance of using molecular diagnostic tests to accurately rule out WD. Ursodeoxycholic acid reduces urinary copper and liver copper content in MDR3 deficiency (50).

ATP7A-related copper transport disorders

ATP7A-related copper transport disorders, caused by X-linked mutations in the *ATP7A* gene, manifest as Menkes disease (MD), occipital horn syndrome, or X-linked distal motor neuropathy, with varying onset ages. MD, a severe systemic disorder due to copper deficiency in organs like the brain and liver, presents with connective tissue abnormalities, kinky hair, progressive neurodegeneration,

and typically death by age three (76). Atypical MD (5–10% of cases), associated with partially functional ATP7A, is milder, featuring longer survival, cerebellar ataxia, and developmental delay. Brain MRI reveals T2-weighted high signal intensity and abnormal copper deposition in the basal ganglia, particularly the globus pallidus, resembling WD. Overlapping phenotypes with WD, due to shared copper transport defects, necessitate *ATP7A* genetic screening in WD-like cases lacking *ATP7B* mutations (77).

Important clinical findings in differential diagnosis

Early laboratory diagnosis of WD often relies on several key clinical findings. These include decreased serum ceruloplasmin and copper levels, increased 24-hour urinary copper excretion, and elevated liver enzyme levels. Combining these various laboratory parameters is crucial for an accurate WD diagnosis, and careful attention to them is highly beneficial (78). For instance, patients with Idiopathic Copper Toxicosis (ICT), characterized by significant copper accumulation in the liver and early-onset severe liver abnormalities, are frequently misdiagnosed as having WD initially. However, their laboratory results typically show normal or elevated ceruloplasmin levels, leading to the exclusion of WD as a diagnosis (79).The Kayser-Fleischer (KF) ring, an important diagnostic marker for WD, is a frequent ophthalmologic finding. It is present in nearly 100% of neuropsychiatric patients, approximately half of those with hepatic manifestations, and about 20-30% of presymptomatic individuals (14). Initially associated with WD in 1912, the KF ring has served as a robust diagnostic feature. However, over the last three decades, it has been observed in several other disorders, leading to a decrease in its diagnostic specificity (80). In cases where neuropsychological symptoms are absent or only liver involvement is present, additional examination and caution are necessary. Consequently, the KF ring is no longer considered a definitive diagnostic marker for WD. Among other disorders where the KF ring has been reported, we can mention chronic cholestatic disorders, monoclonal gammopathies, arcus senilis, and multiple myeloma (81-83). Another less common ophthalmologic finding in WD is sunflower cataract, which occurs in approximately 17% of patients. Fortunately, neither cataracts nor KF rings affect vision and tend to disappear with treatment (84).

In WD, abnormalities in biliary copper excretion can result in elevated liver enzyme levels, which may persist for up to six months in asymptomatic individuals. Physicians often consider chronic hepatitis as a possible diagnosis in such cases, which can be caused by various factors, including Hepatitis B and C. However, recognizing WD as the most common inherited liver disorder can facilitate early diagnosis of this treatable condition (85). WD is often diagnosed with significant delays, partly due to the variability in neurological manifestations and early misdiagnoses. However, since WD is a treatable condition, early diagnosis and differentiation from other neurological disorders are crucial. Several neurological disorders can mimic WD, including young-onset Parkinson's disease, essential tremor, and generalized dystonia. In rarer cases, conditions like Huntington's disease, chorea-acanthocytosis, Hallervorden-Spatz disease, and benign familial chorea may also present with features resembling Wilson's disease (16). Therefore, in such instances, considering WD in the diagnostic process is essential. Psychiatric presentations in WD patients can also resemble other psychological disorders, such as schizophrenia, mood disorders, or drug abuse. However, paying attention to additional diagnostic clues, such as KF rings and liver manifestations, can guide us toward the correct diagnosis. Furthermore, psychiatric symptoms like schizophrenia and sleep disorders can serve as warning signs for WD, emphasizing the importance of considering them to expedite diagnosis (19, 86).

Perspective and future directions

The increasing recognition of WD mimics underscores the urgent need for improved and integrated diagnostic methods. As genetic testing becomes more available, incorporating whole-exome and whole-genome sequencing into conventional evaluations may enhance diagnosis precision, especially for rare or overlapping illnesses. Advancements in neuroimaging, particularly AI-enhanced MRI analysis and radiogenomics, offer possible methods for distinguishing WD from similar disorders through detailed structural and biochemical markers. AI-enhanced radiogenomics offers a novel and promising direction for improving the diagnosis, prognosis, and personalized management of WD. Although WD has not been the primary focus in much of the existing radiogenomic literature, the methodologies and analytical frameworks developed for other neurodegenerative conditions such as Alzheimer's and Parkinson's disease are highly applicable. Recent multiparametric MRI studies have demonstrated that patients with WD exhibit elevated values of fractional anisotropy (FA), mean diffusivity (MD), and magnetic susceptibility in deep gray nuclei, such as the globus pallidus, putamen, thalamus, and substantia nigra, even in the absence of overt lesions on conventional MRI. These quantitative imaging metrics show strong correlations with neurological severity as assessed by the Unified Wilson's

Disease Rating Scale (UWDRS) and are associated with specific clinical features such as tremor, dystonia, dysarthria, and parkinsonism. Leveraging artificial intelligence, particularly deep learning models like convolutional neural networks (CNNs) and autoencoders, enables the automated extraction and interpretation of these complex imaging features and their integration with genetic and epigenetic profiles, including *ATP7B* mutations. This approach enhances early and non-invasive detection of disease-related microstructural changes, facilitates genotype-phenotype stratification, and supports individualized treatment planning, such as monitoring response to copper-chelating therapies. Ultimately, AI-enhanced radiogenomics has the potential to redefine the diagnostic paradigm in WD by providing a data-driven, high-resolution, and clinically actionable framework (87, 88). Recent advancements in deep learning and genetic analysis have significantly enhanced the diagnosis of WD. The WilsonGenAI tool, utilizing the TabNet deep learning model, has demonstrated exceptional performance in classifying *ATP7B* variants as pathogenic or benign, achieving 99% accuracy on validation sets and 97.24% on test sets, with an AUC of 0.996, leveraging the comprehensive WilsonGen database with 723 manually annotated exonic variants. This approach outperforms traditional methods like CADD and other ACMG-based models, offering rapid and accurate variant classification to aid early diagnosis, genetic counseling, and reclassification of variants of uncertain significance, thus supporting clinical decision-making and personalized treatment strategies (89, 90). In future clinical practice, a multi-tiered diagnostic algorithm integrating clinical presentation, copper metabolism markers, advanced imaging, and genetic analysis will likely become the standard paradigm. Furthermore, the development of disease-specific biomarkers, such transcriptomic or proteomic signatures, may enable non-invasive differentiation of WD from analogous conditions, hence reducing diagnostic delays.Precision medicine approaches tailored to individual genetic profiles and metabolic processes may improve therapeutic efficacy and prognosis. Gene editing tools such as CRISPR/Cas9, while still experimental, have the potential to correct *ATP7B* mutations or modulate related pathways in WD and similar conditions. Collaborative multicenter studies and global registries are essential for collecting high-quality longitudinal data, identifying novel variants, and improving genotype-phenotype correlations to achieve these goals. Ultimately, these efforts will improve diagnostic accuracy and patient outcomes while also deepening our understanding of copper metabolism and its related diseases.Notwithstanding the comprehensive nature of this review, many limits must be recognized. The infrequency of WD and its mimicry conditions constrains the feasibility of extensive, longitudinal studies, resulting in dependence on case reports and small cohort studies, which may hinder generalizability. Secondly, the diagnostic criteria and biochemical thresholds for numerous mimic illnesses are developing and among institutions, complicating cross-study comparisons. Furthermore, although the study includes recent advancements in molecular genetics and neuroimaging, swift progress in these domains may have rendered certain diagnostic methodologies obsolete. Ultimately, owing to the variability of WD characteristics and their overlap with other metabolic or neurodegenerative conditions, several clinical distinctions mentioned may not be universally applicable across various populations or age demographics. Future prospective investigations employing standardized diagnostic techniques are necessary to validate and enhance the distinctions presented in this study. The diagnosis of Wilson's disease presents a significant challenge due to its extreme clinical heterogeneity and overlap with other disorders. Increasing awareness and understanding of the diverse phenotypes associated with WD, their age of onset, and the neuropsychological aspects are crucial for accurate clinical diagnosis. Additionally, recognizing disorders that mimic WD is essential. Modern molecular diagnostic techniques, such as NGS, have improved the diagnostic rate by identifying disease-causing variants in the *ATP7B* gene. However, it's important to note that molecular analysis alone is not a screening test for WD. It should be performed only when clinical suspicion exists (e.g., altered copper metabolism, extrapyramidal symptoms, or unexplained liver disease). Screening tests are valuable for individuals suspected of having WD. These may include blood copper and ceruloplasmin studies, 24-hour urine copper excretion measurements, abdominal ultrasonography to assess the liver, and OCT or slit lamp examination to detect KF rings. Considering the wide clinical heterogeneity of Wilson's disease, we recommend considering WD diagnosis for all young patients with a family history of neuropsychiatric disorders, personality and behavior changes, jaundice, and extrapyramidal symptoms.

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