Current Neurology and Neuroscience Reports (2025) 25:40
https://doi.org/10.1007/s11910-025-01424-8

REVIEW

Pitfalls in the Diagnosis of Wilson Disease

Debasish Roy[1] · Angshuman Mukherjee[1] · Ambar Chakravarty[1]

Accepted: 8 May 2025

Abstract

Purpose of Review Wilson disease (WD), an uncommon autosomal recessive (AR) hereditary disorder characterized by abnormal accumulation of copper primarily in the liver and secondarily in other organs like the brain, is caused by a deficiency in the *ATP7B* transporter gene. The key to successful therapy is early diagnosis.

Recent Findings Mutant genes need to be inherited from both parents for phenotypic expression. The *ATP7B* gene located on chromosome 13q14.3 comprises 20 introns and 21 exons, encodes a protein of 165 amino acids, and this helps in incorporation of copper into ceruloplasmin, the copper binding protein. So far, more than 800 mutations have been reported, of which 380 have confirmed involvement in the pathogenesis of WD. The most common mutations are H1069Q and R778L in European and Asian populations respectively. Approximately 90%-98% of WD subjects are heterozygous, showing different mutations in each of the alleles encoding the *ATP7B*. Conversely, the phenotype and the penetrance of WD can be extremely variable. Even patients carrying two disease-causing mutations do not necessarily have a demonstrable alteration of copper metabolism. Considering the possibility of late-onset disease, asymptomatic cases, and phenotypic variability, it is crucial to evaluate previous and future generations of the index case.

Summary WD ranges from being asymptomatic in some patients to result in acute liver failure and/or a variety of neuropsychiatric disorders among others. Although WD may be present at any age, is more common between the ages of 5 and 35 years. However, it should be investigated in patients with liver failure of unknown cause and those with liver disease associated with neuropsychiatric symptomatology. Diagnosis requires a combination of clinical signs and symptoms, as well as relevant diagnostic tests such as measurement of serum ceruloplasmin, urinary excretion of copper, liver biopsy or genetic testing. Treatment is lifelong and includes chelating agents (penicillamine and trientine) and inhibitors of copper absorption (zinc salts). Liver transplant is an option for patients with end-stage liver disease. The key to successful therapy is early diagnosis.

Keywords Wilson disease · Ceruloplasmin · Serum copper · Urinary copper excretion · Genetics · Neurological pitfalls · MRI in Wilson disease

Introduction

Wilson disease (WD), is a genetically determined and treatable neurometabolic disease. The causative *ATP7B* gene is located on chromosome 13q14.3. It comprises 20 introns and 21 exons, encoding a protein of 165 amino acids [1–8]. This helps in the incorporation of copper into ceruloplasmin, the copper binding protein. So far, more than 800 mutations have been discovered in the gene [6]. Of these 380 have confirmed involvement in the pathogenesis of WD [8, 9]. Although mutations have been reported in almost all exons [5], they mainly affect the central regions of the gene (both 8 and 14 exons are the most frequently affected). The most common mutations are H1069Q and R778L in European and Asian populations, respectively [2, 4]. Approximately 90%−98% of WD subjects are heterozygous, showing different mutations in each of the alleles encoding the ATP7B. Conversely, the phenotype and the penetrance of WD can be extremely variable. Even patients carrying two disease-causing mutations do not necessarily have a demonstrable alteration of copper metabolism [7]. Hence, the potential role that epigenetics could have in the gene expression of the disease needs to be looked into. Considering the probability of late-onset, the fact of having asymptomatic cases, and the phenotypic variability, it seems vital to evaluate the previous and next generation of the index case [8]. Some of the

✉ Ambar Chakravarty
saschakra@yahoo.com

[1] Department of Neurology, Vivekananda Institute of Medical Science, Kolkata, West Bengal, India

Published online: 12 June 2025

proposed reasons are differences in copper intake, individual antioxidant capacity or susceptibility to liver fibrosis, and hormonal influences [9].

Early diagnosis is of paramount importance. Treatment delays risk unfavorable outcomes [10–14]. WD is caused by a mutation in the gene that encodes a copper-transporting P-type ATPase (*ATP7B*). This gene product transports excess copper into bile and thus is excreted in the small bowel. WD is an AR disorder. Most mutations are missense mutations, small deletions/insertions in the coding region, or splice junction mutations. Rarely, whole exon deletions and promoter region mutations have been found. *ATP7B* mutation "hot spots" vary considerably among different populations [8, 9, 14, 15]. Diagnosis of WD remains challenging because it is a great imitator [1, 10–14, 16].

Causes for delay in diagnosis are multiple. Walshe and Yealland [13] highlighted three major reasons: underestimation of subtle early clinical features like tremors or writer cramps; suboptimal awareness of the condition; and lastly, laboratory errors in the estimation of copper and ceruloplasmin concentrations. Evaluation for Kayser-Fleischer (KF) rings should be done by experienced ophthalmologists, using a slit lamp. KF rings should be differentiated from arcus senilis/juveniles, by its position in relation to the Descemet membrane at the limbus. Of note, KF rings may not be present when WD manifests with non-neuropsychiatric features. Patients presenting with psychiatric symptoms often receive antipsychotic agents and with the development of extrapyramidal symptoms with disease progression, a hallmark of WD, these may be misinterpreted as drug related adverse events. It is also known that even after suggestive laboratory markers (like low ceruloplasmin levels), starting appropriate therapy is delayed. Inadequate knowledge regarding long term management, non-availability of drugs in certain centers, financial issues, inappropriate counseling, and need for prolonged treatment are the main culprits [3, 4].

Neurologic problems at onset are seen in approximately 40%–50% of patients. The remainder present with either hepatic or primarily psychiatric manifestations. Neurologic and neuropsychiatric problems are quite non-specific and the most common clinical problems associated with early and late stages of the disease. Patients with neurologic symptoms may not always have obvious hepatic symptoms. Dysarthria, dystonia, tremor and parkinsonism are the most common neurologic abnormalities. Regardless of the clinical heterogeneity observed in many patients with WD, laboratory abnormalities reflecting abnormal copper metabolism, are very specific and the diagnosis of WD, essentially remains laboratory based. The clinical picture may be mimicked by several basal ganglia disorders both during the acute and chronic stages of the disease. There also can be pitfalls in standard laboratory tests used in the diagnosis. This has necessitated the application of genetic studies for diagnostic confirmation. There again errors may occur as new sites of mutations have been recently described which produce phenotypically similar clinical presentations. Treatment had been standardized with the use of copper chelators to induce a negative copper balance state but at times drug therapy may induce further clinical deterioration in some treated patients.

Most patients develop symptoms in adolescence to early adulthood. Neurologic symptoms generally develop approximately one decade after hepatic presentation. Age of onset may be variable with late disease onset noted even in the 7 th and 8 th decades of life. This may cause considerable diagnostic challenges because clinical symptoms are like other common, age-related conditions like parkinsonism. Initial signs and symptoms of WD are liver related in approximately 40% of patients, neurologic in about 40%–50% and primarily psychiatric in about 10% of patients [2, 3]. WD may be diagnosed in presymptomatic individuals through biochemical screening of siblings of affected individuals or in asymptomatic individuals when routine laboratory test detects otherwise unexplained abnormalities of liver function tests. Patients presenting with liver disease may range from asymptomatic to life-threatening hepatic failure. Most patients with hepatic symptoms have chronic splenomegaly due to portal hypertension and Coombs-negative hemolytic anemia [3, 5].

Neurological Diagnostic Pitfalls

Early neurologic symptoms are generally subtle and nonspecific. Troubles with concentration are particularly common. Motor symptoms include lack of coordination, handwriting changes, and slurred speech with drooling [3]. A primarily psychiatric disorder is often misdiagnosed before the correct diagnosis is reached with potentially catastrophic consequences. In such cases, the course is progressive and more severe neurologic abnormalities emerge—dysarthria, dystonia, tremor and parkinsonism being most common. At times, tremor and ataxia may develop early in the disease, followed by dystonia and parkinsonism. Neurologic phenotype in WD has been grouped into dystonic, pseudo-sclerotic (tremor), parkinsonian and hyperkinetic (choreatic) subtypes [5]. Dysarthric forms have also been suggested, but dysarthria is the most constant neurologic sign in WD. 90% of affected individuals have speech abnormalities in the course of the disease [5, 7].

Dysarthria is often mixed with dystonic and hypokinetic features. Patients with the pseudo-sclerotic phenotype may also exhibit signs of cerebellar ataxia and cerebellar dysarthria. However, there is a considerable overlap among these groups and patients with severe WD display a mixed phenotype [5].

Tremor is another common presenting symptom in patients with WD [15]. The wing-beating tremor is a proximal tremor, which appears when patients hold their semi-flexed arms outstretched. This has been suggested as a hallmark tremor of WD, though it may not be present in many patients. The tremor increases in amplitude with a longer duration of posture holding, ultimately progressing to a severe flapping tremor with large amplitudes [17].

Focal or generalized dystonia may occur in about a third to half of patients in the early stage of the disease [1, 5, 7]. Segmental or focal dystonia affecting the cranio-facial musculature may be very troublesome with severe dysphonia, and dysarthria. At times there is complete loss of speech, *risus sardonicus* with exaggerated smile and dysphagia progressing to total inability to swallow food. Focal dystonia in one limb manifesting as writer's cramp is not very uncommon among young subjects. Advanced WD may be associated with generalized dystonia, with debilitating symptoms, secondary skeletal changes and inability to walk. The dystonia observed in WD is a secondary dystonia, with hyperkinetic jerks being less common than in idiopathic primary dystonia [5].

A hypokinetic-rigid syndrome may be present in about a third to half of patients presenting with an impassive facies along with a hypophonic voice, micrography and shuffling or gait freezing [3]. Such parkinsonian symptoms are generally symmetrical but unilateral tremor can be observed. This phenotype needs to be distinguished from Parkinson disease (PD) occurring in younger subjects and from the akinetic rigid form of Huntington disease in the young (Westphal variant).

Uncommonly, choreoathetoid movements may be noted. True cerebellar ataxia and incoordination and balance problems are more commonly caused by extrapyramidal system affection [1, 3, 7]. Of course, tremor in WD may have some cerebellar features like dysmetria and intention tremor.

Seizures in WD

A large Indian study [17[noted that seizures precede symptoms related to WD in about 20%, occur concurrently in around 50%, and follow copper chelating therapy in about 30% of cases. Most seizures are generalized tonic–clonic (GTC) in nature. Interictal EEG abnormalities are common. Brain MRI may show signal changes especially in the white matter but also in the basal ganglia. It has been postulated that deafferentation of white matter tracts from the cortex may be the cause. Autopsy studies may show cavitary lesions in the white matter in the frontal, temporal and parietal areas with varying involvement of the cortical ribbon. A few cases of status epilepticus have also been described mostly after starting copper chelation therapy [18]. Most patients had focal onset seizures with secondary generalization on ictal electroencephalographygraphy. New onset seizures in young patients need to have their ceruloplasmin levels checked.

Psychiatric Pitfalls

Presentation with psychiatric symptoms is probably the most important cause of delayed diagnosis in WD due to the non-specific nature of the symptoms.

Case Vignette: *A 32-year-old sailor had been referred to the corresponding author (AC) for neurological assessment by a psychiatrist in 2011. This man was diagnosed to have bipolar disorder for which he was been treated with valproate sodium and a selective serotonin reuptake inhibitor. His mood improved, but of late, he was found to be slow in motor tasking and with tremor of both hands. These features were attributed to parkinsonism related to valproate therapy. The valproate was stopped and replaced with carbamazepine. After two months of being off valproate, his condition deteriorated. This prompted a neurological referral. On examination he was found to have symmetrical parkinsonian features with tremor, rigidity and bradykinesia. Eye examination demonstrated the presence of a brownish ring at the limbus of both eyes. Slit lamp examination confirmed presence of KF ring. The serum ceruloplasmin level was much low (7 mg/dl) and his liver enzymes were mildly raised. WD was diagnosed and he was started on D-Penicillamine and zinc sulfate. His condition improved over the next six months. Later his psychiatric treatment could be tailed off. He continues to remain well till date. His KF rings had disappeared after about six years of therapy.*

A younger brother, 30 years of age, was asymptomatic. A KF ring was seen in both of his eyes. The serum ceruloplasmin was low as well. This suggested the diagnosis of asymptomatic WD. He was also started on D- Penicillamine and he remains asymptomatic until this day. The KF ring had disappeared several years earlier.

Often noted psychiatric disturbances of WD include behavioral and personality disorders. Common manifestations include irritability, aggression, and antisocial behavior. Catatonia, anorexia nervosa, bulimia, obsessive–compulsive disorder and attention-deficit hyperactivity disorder have also been reported [2, 5, 7]. The first psychiatric manifestation may even occur in childhood as a decline in school performance, inappropriate behavior or impulsivity. Paradoxically, psychiatric symptoms may become evident following the institution of chelation therapy when the neurological features are improving. Mood disturbances are the most common psychiatric manifestation especially severe depression, often combined with a high rate of suicidal ideation and attempts. Bipolar disease is encountered in patients WD more frequently than in age and gender matched controls. The neural basis of such features as emotional lability,

irritability and aggression, shallow cheerfulness, euphoria, social disinhibition, hypersexuality, and deficits in planning and anticipating social consequences, have been postulated to be due to involvement of frontal lobe or its pathways related to copper deposition.

When psychotic symptoms occur as the first manifestation of WD, both diagnostic and therapeutic challenges face the clinician. Very often such symptoms are due to schizophrenia, schizoaffective or delusional disorder. Some guidelines suggest exclusion of WD in first episodes of psychosis [2]. Onset of WD with psychiatric symptoms often causes delay in diagnosis.

Neuromuscular Pitfalls

A rare diagnostic puzzle is when children present with proximal limb muscle weakness, which may be mistaken for a primary muscle disease.

Case Vignette: *A 7-year-old child had slowly progressive weakness of both proximal lower limb muscles with difficulty in walking, climbing stairs and rising up from a squatting position. Symptoms had been present for approximately two months. She had muscle pain or cramps. There was no family history of similar disorders. On examination, she was a thin built child who walked with a waddling gait and had considerable difficulty in getting up from squatting position though she did not exhibit the typical Gower sign. Cranial musculature, neck musculature and upper limbs were of normal power. In the lower limbs, muscle power was reduced in the quadriceps, hamstrings and the glutei (power grade 3+—4 MRC) but were normal in the distal leg and feet muscles. She could stand on her toes and heels. Muscle stretch reflexes were intact. Plantar responses were flexors. No sensory changes were elicitable including intact joint position sense and vibration. She had mild hepato-splenomegaly. Hemogram, ESR, urea, creatinine, electrolytes (including* Ca^{++}*) and serum CK were normal. Serum alkaline phosphatase was raised above the upper limit of normal for a child. Facilities for estimating Vitamin D3 and B12 were not available at that time. EMG/NCS did not show any spontaneous activity nor any myopathic changes. Nerve conduction studies were normal. A muscle biopsy was planned.*

On the third night after admission, she had a bout of hematemesis. This was managed with one unit of packed cell transfusion. A barium swallow of the esophagus showed presence of esophageal varices. Ophthalmological examination demonstrated the presence of a brownish ring at the scleral-corneal junction suggestive of a KF ring. Serum ceruloplasmin was down to 8 mg/dl. A liver biopsy showed liver cirrhosis. WD was confirmed. She was sent home on a small dose of D-penicillamine but was lost to follow-up.

Very few such cases have been recorded in the literature, but this had been recognized in South Asian countries [19, 20]. The exact pathophysiology of the early proximal muscle weakness observed is not known. However, it may be speculated that this is in some way related to the calcium metabolism in these patients as hypocalcemia had been observed in some WD patients related probably to the association with hypoparathyroidism and possibly with the renal tubular dysfunction, observed in some patients [20].

Other systemic manifestations of WD, including aminoaciduria, nephrolithiasis, arthropathy, premature osteoporosis and cardiomyopathy, are rare and very difficult to be recognized as the result of WD without other features of the disease.

Laboratory Diagnostic Pitfalls

The first step for confirming the diagnosis in suspected cases of WD is a serum ceruloplasmin level less than 20 mg/dL (1.49 µmol/L) which has an overall positive predictive value of less than 6% [21]. Ceruloplasmin is the main copper binding plasma protein with more than 90% of total copper bound to it. However, even low ceruloplasmin levels cannot conclusively confirm the diagnosis of WD and additional confirmatory tests need to be performed [3–7]. Ceruloplasmin being an acute phase reactant, may reveal false negative data, leading to a missed diagnosis of WD. An important cause of higher ceruloplasmin is elevated estrogen levels, often caused by oral contraceptives or estrogen replacement therapy. Abnormally low ceruloplasmin level less than 5 mg/dl (0.37 µmol/L), though strongly suggestive of WD can also be found in conditions with very low serum copper levels, in copper deficiency states and aceruloplasminemia [21, 22]. Genetic disorders of copper metabolism that might mimic WD include [6, 7]:

1. **Menkes disease**: This X-linked recessive disorder is characterized by impaired copper absorption due to mutations in the *ATP7 A1* gene Menkes disease typically occurs in boys aged 2–3 months and is characterized by neurodevelopmental delay, seizures, and failure to thrive [23, 24]. Death usually occurs within a few years after onset. Early treatment with parenteral copper is indicated at diagnosis.
2. **Occipital horn syndrome**: This is a mild variant form of Menkes disease, characterized by milder neurological manifestations, slight generalized muscle weakness, dysautonomia, and chronic diarrhoea. Diagnosis is usually delayed due to the non-specific nature of symptoms.
3. **Distal motor neuropathy**: Features include: *ATP7 A* allelic variant, progressive distal motor neuropathy and no overt copper metabolic abnormalities

4. **Huppke-Brendel syndrome**: This disorder is related to mutations in *SLC33 A1* which encodes the acetylCoA transporter AT-1. There is low serum copper and ceruloplasmin concentrations. Patients have congenital cataracts, hearing impairment, severe developmental delay, pronounced cerebellar hypoplasia and hypomyelination [25].
5. **5. MEDNIK syndrome** (acronym—Mental retardation, Enteropathy, Deafness, Neuropathy, Ichthyosis, and Keratoderma). This is an autosomal recessive trait due to mutations in the *AP1S1 gene* (encodes the σ 1 A small subunit of the adaptor protein complex-1 (AP1), that is involved in the intracellular trafficking of transmembrane proteins; hypo-cupremia, hypo-ceruloplasminemia and hepatic copper accumulation, similar to that seen in WD [26].
6. **Aceruloplasminemia**: This is a rare autosomal recessive neurodegenerative disease, usually presenting during late adulthood around age 50–60 [27, 28]. It belongs to the group of *Neurodegeneration with Brain Iron Accumulation*, particularly in the basal ganglia and liver. There is a complete lack of ferroxidase activity in the case of homozygous mutation. The serum indicates a low level of copper and iron with elevated ferritin. Renal copper excretion is normal. Neurological features include ataxia, dysarthria, hyperkinesias, dystonia, parkinsonism, depression and cognitive disorders. Anemia, retinopathy, diabetes mellitus and in some patients, heart failure due to iron overload are the cardinal systemic features. Heart failure is the major determinant of prognosis.
7. **Defects in copper metabolism** are also seen in some children with congenital disorders of glycosylation, often accompanied by severe liver disease.

A 24-h urine copper excretion can confirm the diagnosis of WD in patients with neurologic symptoms who do not have advanced obstructive liver disease [22]. Complete collection of 24 h must be ensured, and the collecting vessel must not be made of copper. The 24-h copper excretion values more than 100 µg are conventionally considered diagnostic of WD. While this may be true for patients with neurologic or psychiatric clinical presentations who have no signs of chronic cholestasis, in normal individuals, the 24-h urine copper excretion is generally below 40 or 50 µg. Values below this cutoff would exclude WD. Intermediate values between 50 and 100 µg may be seen among heterozygous (carriers) individuals. Symptomatic children with WD may also have 24-H urine copper values below the conventional 24-h urine copper. Urinary excretion test can also be used for therapy monitoring. In doubtful cases, a significant rise in copper excretion after a challenge dose of D- penicillamine, may be used as suggestive of WD [2].

Serum non–ceruloplasmin bound or free copper assay is often used as a diagnostic test for WD along with estimation of ceruloplasmin. It is elevated above 25 ug/dL in most untreated patients. However, raised levels may also be seen in acute liver failure. Normal values are 10–15 µg/dL and free copper below 5 µg/dL, indicates copper deficiency. It is not advisable to rely on total copper value alone, as it is very variable and generally parallels the value of the main copper binding protein—ceruloplasmin [22, 23].

Liver biopsy has been considered the gold standard for the confirmation of the diagnosis of WD and may still be required in patients with predominantly hepatic presentation. The diagnosis of WD with neurological and/or psychiatric presentations, can be reliably based on diagnostic values of 24-h urine copper excretion along with a low serum ceruloplasmin level.

Ophthalmologic Diagnosis

The presence of KF rings caused by copper deposition in the Descemet membrane of the cornea at the sclera-corneal junction, is often considered as diagnostic of WD, when combined with a low ceruloplasmin level [1, 2]. Naked eye examination may reveal a golden-brownish pigmentation around the limbus [2]. Ophthalmoscopic examination with a 10 diopters lens to get a magnified view of the limbus region, would be a better way to detect such a ring. Some rings may be incomplete, and increased pigmentation can be seen around 6 and 12 o'clock positions only. Definitive detection of KF rings can be made using slit lamp. Development of sunflower cataracts caused by copper deposits in the lens can also be detected through a slit lamp examination. It may be noted that the presence of rings can only support the diagnosis of WD as such rings can rarely be seen in patients with chronic cholestasis. Also, KF rings may not be visible in WD patients with only the hepatic form of the disease. Absence of KF rings is rare (in only 10%) in patients with neurologic presentations [16]. Copper deposits in the cornea and the lens disappear with chelation therapy. Initially, KF was considered pathognomonic for WD. However, they are rarely found in primary biliary cholangitis, chronic cholestasis or in children with neonatal cholestasis. Regarding differential diagnoses, corneal opacities caused by other diseases, such as galactosialidosis. Despite these aspects, KF rings are considered a classical ophthalmological manifestation of WD, while the sunflower cataract caused by copper accumulation in the lens of the eye is rare.

Abdominal WD

Abdominal features in WD include hepatomegaly, jaundice, right upper quadrant pain, asthenia, elevation of liver transaminases, acute liver failure, cirrhosis and steatosis.

Combined jaundice and anemia, especially in toddlers up to puberty are, in addition to WD, significant in regard to differential diagnoses. Amongst others, hemoglobinopathies, iron deficiency, lymphatic leukaemia, erythroblastopenia, glucose-6- phosphate dehydrogenase deficiency and autoimmune hemolytic disorders must be taken into consideration. In the Indian subcontinent, iron deficiency anemia and thalassemia minor account for most causes o anemia in children and adolescents. It is important to include estimation of serum ceruloplasmin level in the work-up of children up to puberty with hepato-splenomegaly and with icterus specially. In very young children with hepatic failure, it is also important to exclude WD when the viral hepatitis panel is negative. Indian Childhood Cirrhosis used to be considered in the differential of WD in toddlers, but fortunately this disease seems to have been extinct. Its cause and reason for its disappearance remains unclear though improved nutritional status may be one of the causative factors.

Pitfalls In Genetic Diagnosis

Molecular genetic testing with sequencing of the *ATP7B* gene is confirmatory of the diagnosis of WD if both disease-causing mutations can be identified [5, 15]. Allelic heterogeneity in WD is common with many mutations being limited to single families and most patients exhibit compound heterozygote states. Therefore, unless mutations in the specific family are known or the patient is from a region where certain mutations are very commonly encountered, all exons and promoter regions must be sequenced. This would necessitate targeted mutation analysis for specific mutations prevalent in the population concerned with PCR [29]. Overall rate of detection of mutations in patients with biochemically confirmed disease is about 98% but intronic mutations or mutations in the promoter regions, may remain undetected. Hence a negative genetic testing alone, would not absolutely exclude WD. Supportive biochemical laboratory testing are mandatory.

Progressive familial intrahepatic cholestasis type 3 (PFIC3, OMIM #602347, gene ABCB4) is an autosomal recessive cholestatic liver disorder caused by absence of functional multidrug resistance protein 3 (MDR3), also known as ATP-binding cassette (ABC) subfamily B member 4 (ABCB4) [30]. ABCB4/MDR3 is a hepato-canalicular transporter, "floppase (a protein that moves lipids from the cytosolic side of a membrane to the exoplasmic side), translocating phosphatidylcholine from the inner leaflet to the outer leaflet of the canalicular membrane lipid bilayer. The effects of ABCB4 deficiency on hepatobiliary system can be related to "toxic bile" with potent detergent and lithogenic properties. Typical laboratory findings include conjugated hyperbilirubinemia and elevated serum γ-glutamyl transferase (GGT) activity. Chronic cholestasis is often associated with increased urinary copper excretion and significant deposition of copper in the liver. This may be misinterpreted as Wilson's disease (hepatic form) in liver biopsy specimens.

Pitfalls/Differentials in Neuro-Radiological Diagnosis

Magnetic resonance imaging (MRI) can detect structural abnormalities in the majority of WD patients with neurologic presentation. The most common finding is hyperintensity on T-2 weighted and FLAIR images involving the putamen, striatum and globus pallidus. These along with hyperintense signals in the midbrain around the red nucleus and substantia nigra may give the appearance of "eye/face of giant/little panda sign" that is most commonly observed in WD patients. However, these changes are non-specific and WD needs to be confirmed by other laboratory methods. MRI changes correlate with neurologic deficits and clinical improvement with chelation therapy also followed improvement in the signal changes detectable with serial MRIs. Structural changes also correlate with cognitive decline in these patients [31, 32]. In WD, functional assessment of dopaminergic innervation using single photon emission computerized tomography (SPECT) in striatum may be abnormal using both presynaptic and postsynaptic dopaminergic markers. This pattern is nearly specific for WD because in other striatonigral neurodegenerative disorders, either pre or postsynaptic deficits can only be noted but not of both. Some patients with chronic hepato-cerebral degeneration associated with liver cirrhosis with cognitive and gait dysfunction often exhibit similar MRI changes to WD. Similar features are also seen in cases with chronic manganese toxicity (seen among mine workers). The differential features are tabulated in Table 1.

Therapeutic Paradox/Pitfalls

Case Vignette:*A 12-year-old boy presented in March1995 at the neurology clinic with history of progressive scholastic deterioration, behavioral problems, slurring of speech, drooling of saliva and worsening of handwriting due to dystonic posturing of hands for the past three years. He also had gaze evoked horizontal nystagmus. Clinical diagnosis of WD was made in view of the history, observation of mild dystonia in the hands and the finding of a scleral-corneal ring which was later confirmed as KF ring by slit lamp examination. Family history had been negative, no hepatosplenomegaly or any hepatic dysfunction. The diagnosis was confirmed by the findings of low serum*

Table 1 Differential features of wilson disease, acquired hepato-cerebral degeneration and chronic manganism

WD	Acquired Hepato-cerebral Degeneration	Chronic Manganism
Serum Ceruloplasmin ↓	Abnormal liver function tests	↑ manganese levels in whole blood
24 h urinary copper ↑	Normal to slightly ↑ ammonia level	
Abnormal LFTs	↑ manganese levels in whole blood and CSF may be shown	
Hemolytic anemia +		
Genetic testing: ATP7B mutations		
Imaging: T2-MRI: Hyperintensities in the thalamus, lentiform and caudate nuclei, midbrain (''eye/face of the giant/little panda''),	Imaging:1) T1-MRI: hyperintensities in the globus pallidus, putamen, and substantia nigra 2) T2-MRI: MCP and cerebellum 3) F-DOPA and DAT scan: conflicting results (normal uptake and reduced uptake of F-DOPA and DAT	Imaging:1) T1-MRI: hyperintensities in the globus pallidus and substantia nigra 2) F-DOPA and DAT scan: conflicting results (normal uptake and reduced uptake of F-DOPA and DAT)
Pathology: Opalski cells, Alzheimer type II astrocytes, cavitations	Pathology: Alzheimer type II astrocytes, Poly-micro-cavitation, CPM/EPM	Pathology: Alzheimer type II astrocytes

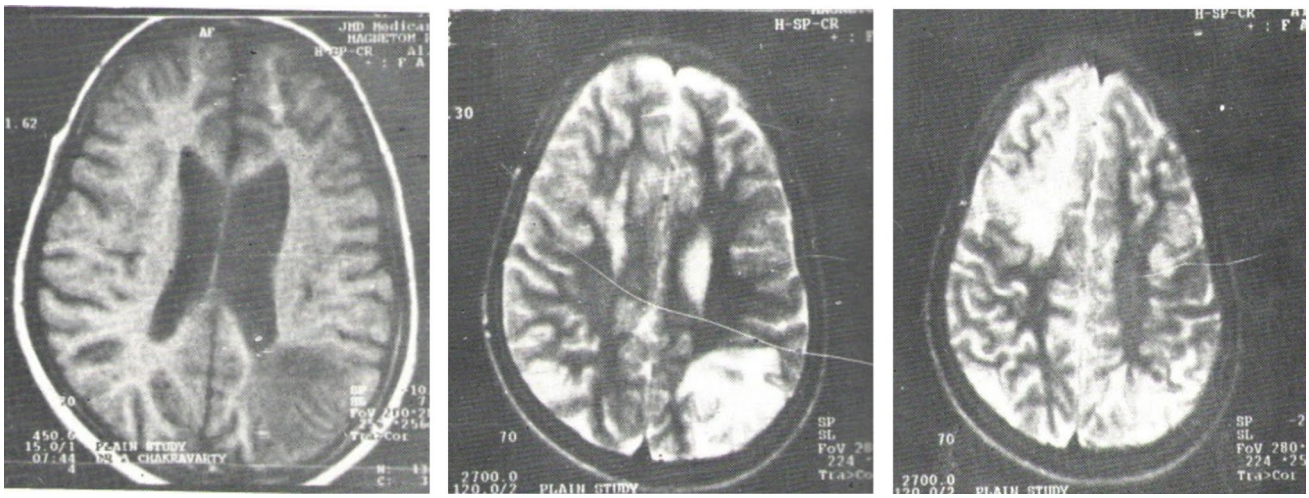
ceruloplasmin level (8 mg/dl) and a high 24-h urinary copper excretion of 138ug (normal upto70ug). Hepatic and renal function tests had been normal. The initial pre-treatment CT scan of brain showed mild ventricular dilatation only. The EEG was normal. Therapy was started with D-penicillamine 250 mg daily which was subsequently increased to 500 mg daily along with Vitamin B6 supplementation. A couple of weeks later zinc sulphate 600 mg daily in divided dosage was added with D-penicillamine. Initiation of therapy had been uneventful and within a fortnight his symptoms started improving with improvement in speech and handwriting. After six weeks of therapy the 24 h copper excretion was88.6ug.

*Suddenly in end June 1995, after 3 months of therapy, he was brought in with development of gross disorientation, recurrent vomiting, increased slurring of speech and hyper-salivation. Though his condition gradually improved in the latter part of the day, similar deteriorations, especially in the mornings continued over the subsequent three days. All medicines were withheld, and he was admitted. He was still disoriented with memory dysfunction, dyscalculia, had increased slurring of speech, rigidity of limbs, central nystagmus but no upper motor neuron signs. Routine hematology, blood biochemistry, liver function tests, serum ammonia and prothrombin time were normal. EEG showed diffuse slowing of the background. This persisted even when repeated one week later. Head CT this time showed hypodense lesions at the right frontal and left parieto-temporal regions. The boy was started on carbamazepine on the suspicion that he probably had had non-convulsive seizures during sleep at night. His clinical condition improved over the next 7–10 days and he was restarted on D-penicillamine and zinc sulfate. MRI of the brain revealed (*Figs. 1, 2 and 3*), multiple asymmetric non-enhancing lesions (T1 and T2 lengthening) involving subcortical and deep white matter in both frontal, left temporal and both parietal regions. Both putamina and thalamic regions showed similar lesions. Focal areas of hyperintensity on long TR images were noted in midbrain and pontine tectum. Both lateral ventricles seemed enlarged (L > R).*

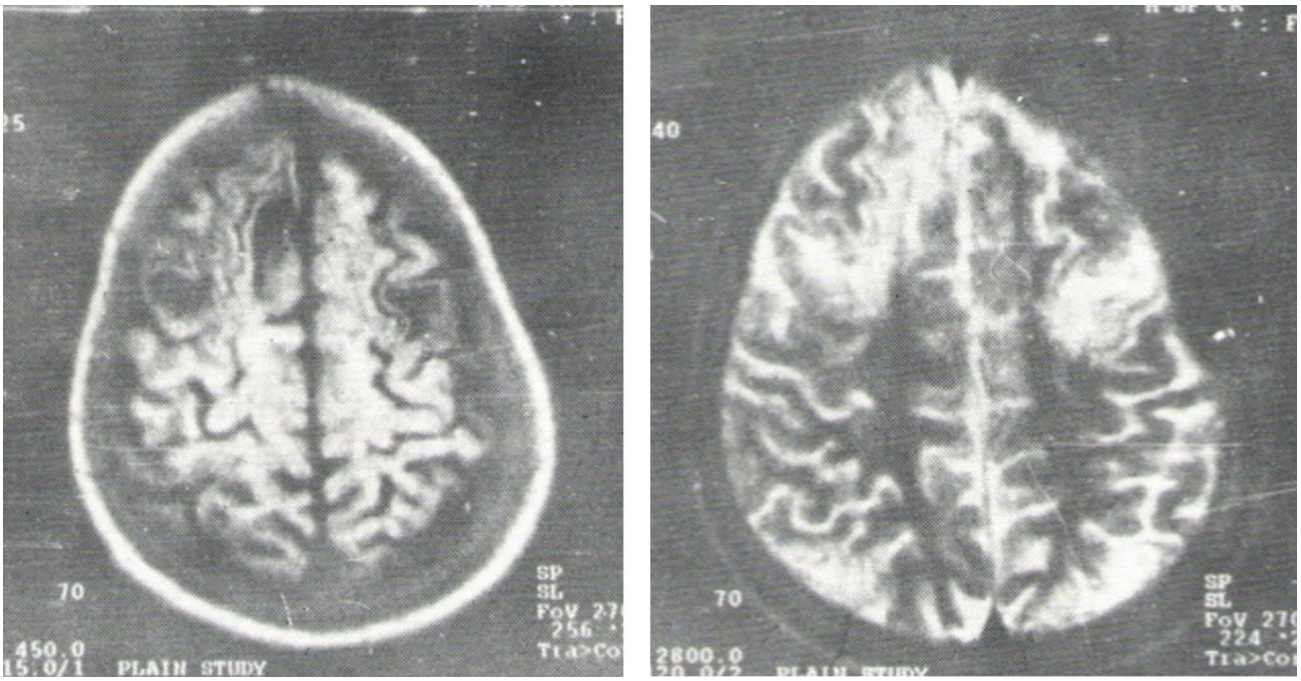
Echocardiography, and detailed connective tissue and coagulation screen were unremarkable.

*The clinical status improved, and he was sent home. He continued D-penicillamine 500 mg daily, zinc sulfate 600 mg daily and carbamazepine 300 mg daily. All his neurological parameters improved. EEG showed persistent of slowing over the frontal and parietal regions of both sides. A repeat MRI of brain (*Figs. 4 and 5*) three months later, revealed gross encephalomalacia in both frontal lobes, left temporal and both parietal lobes. Cavitary changes were noted in the frontal lobes mostly. The signal changes noted earlier in the basal ganglia persisted so also the ventricular dilatation.*

Deterioration of clinical status following successful initiation of therapy with D-penicillamine has been reported in up to 40% of cases [33, 34], but very seldomly observed by us. In the present case, it is likely that there had been very rapid turnover of hepatic copper stores with huge amount of free copper released into the circulation, which the kidneys failed to excrete completely and quickly. The result had been a large amount of free copper getting access to the brain and getting deposited and causing widespread demyelination. There is a report of a presymptomatic patient with WD,



Figs. 1-3 MRI brain during acute phase of the illness showing multiple areas of alterations of signal suggesting encephalomalacia due to copper accumulation



Figs. 4 & 5 MRI brain showing residual encephalomalacia with cavitary changes

becoming neurologically disabled after initiation of therapy with D-penicillamine [34].

Occurrence of such a devastating phenomenon in some subjects with WD, would raise several issues in relation to therapy with chelating agents. No doubt treatment should be started with a lower dosage. But practical problem of providing such a dose remains – capsules are available only containing 250 mg of D-penicillamine and this cannot be halved! The present author practices starting treatment with Zinc sulfate, in a graded manner to minimize copper absorption as much as possible, and then introduce the chelating agent in a small dose, which would perhaps prevent hepatic release of very large amount of copper rather suddenly. Furthermore, the D-penicillamine maybe combined with potassium or ammonium tetra-hydro-molybdate, both of which tend to make free copper 'non-toxic'[35]. It is worth remembering that D-penicillamine has been reported to cause a hypercoagulable state with strokes and excess immune mediated vasculitis conditions like systemic lupus erythematosus (SLE) and Goodpasture syndrome. A further

point needs mentioning – both zinc and penicillamine need to be given separated from mealtime by several hours; also, they should not be given together but again separated by some hours if given together [36], penicillamine would chelate zinc sulphate and reduce its bioavailability.

Conclusions

WD is caused by a mutation in the gene that encodes a copper-transporting P-type ATPase (*ATP7B*). This gene product transports excess copper into bile and thus excreted in the small bowel. Failure of transportation would lead to excess copper accumulating in hepatocytes and then onto brain and other organs. Several non-neurological manifestations of WD occur and their early recognition are of paramount importance. Onset of WD with psychiatric symptoms often causes delay in diagnosis. Children presenting with behavioural and personality disorders including attention deficit hyperactivity disorders must be screened for WD. In the Indian subcontinent, any patient below the age of 50 years, presenting with a movement disorder, however trivial it might be, must be screened for WD. The same may be true for younger patients (< 40 years) presenting with any form of psychiatric disorder as mentioned in the text. Also in the Indian subcontinent, assessment for proximal muscle weakness in children must include tests to exclude WD. Seizures may be the initial presentation of WD. Penicillamine should be started at a very small dose if used as initial therapy for WD with serial measurements of urinary copper excretion. Rapid turnover of hepatic copper may lead to excess copper deposition in brain with clinical deterioration. Deterioration may also occur with red cell deposition causing acute haemolytic crisis. Alternatively initial therapy may be started with oral zinc sulphate or tetra-hydro-molybdate and penicillamine started later when urinary copper excretion stabilizes.

Key References

- Hermann W. Classification and differential diagnosis of Wilson's disease. Ann Transl Med 2019;7(supp2):S63-69
- Aggarwal A, Bhatt M. Wilson disease. Curr Opin Neurol 2020;33(4):534–542.
- Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. J Neurol Neurosurg Psychiatry 1992;55:692–696
- Bandmann O, Weiss KH & Kaler SG Wilson's disease and other neurological copper disorders. Lancet Neurol.2011;4:103–113
- Prashanth LK, Taly AB, Sinha S, Arunodaya GR, Swamy HS. Wilson's disease: diagnostic errors and clinical implications. J Neurol Neurosurg Psychiatry 2004;75:907–909.

Author Contribution All authors contributed equally in the preparation of the manuscript.

Funding Nil.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Hermann W. Classification and differential diagnosis of Wilson's disease. Ann Transl Med. 2019;7(supp2):S63-69.
2. Członkowska A, Litwin T, Dusek P, Ferenci P, Lutsenko S, Medici V, Rybakowski JK, Weiss KH, Schilsky ML. Nat Wilson disease. Rev Dis Primers. 2018;4(1):21–8.
3. Aggarwal A, Bhatt M. Wilson disease. Curr Opin Neurol. 2020;33(4):534–42.
4. Liu J, Luan J, Zhou X, Cui Y, Han J. Epidemiology, diagnosis, and treatment of Wilson's disease. Intractable Rare Dis Res. 2017;6:249–55.
5. Poujois A, Woimant F. Wilson's disease: A 2017 update. Clin Res Hepatol Gastroenterol. 2018;42:512–20.
6. Camarata MA, Gottfried M, Rule JA, Ala A, Lee WM, Todd Stravitz R, Schilsky ML. Outcomes of Acute Liver Injury in Adults Due to Wilson's Disease: Is Survival Without Transplant Possible? Liver Transpl. 2020;26:330–6.
7. Bennett J, Hahn SH. Clinical molecular diagnosis of Wilson disease. Semin Liver Dis. 2011;31:233–8.
8. Chang IJ, Hahn SH. The genetics of Wilson disease. In: Handb Clin Neurol. 2017;142:19-25
9. Li H, Tao R, Liu L, Shang S. Population screening and diagnostic strategies in screening family members of Wilson's disease patients. Ann Transl Med. 2019;7:S59-63.
10. Prashanth LK, Taly AB, Sinha S, Arunodaya GR, Swamy HS. Wilson's disease: diagnostic errors and clinical implications. J Neurol Neurosurg Psychiatry. 2004;75:907–9.
11. Hedera P. Wilson's disease: A master of disguise. Parkinsonism Relat Disord. 2019;59:140–5.
12. Poujois A, Woimant F. Challenges in the diagnosis of Wilson disease. Ann Transl Med. 2019;7(Suppl 2):S67-71.
13. Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. J Neurol Neurosurg Psychiatry. 1992;55:692–6.
14. Bandmann O. Weiss KH & Kaler SG Wilson's disease and other neurological copper disorders. Lancet Neurol. 2011;4:103–13.
15. Lenka A. Jankovic J Tremor Syndromes: An Updated Review. Front Neurol. 2021;12:68483.

16. Chakravarty A. Movement disorders. In: Chakravarty A, editor. Neurology & Internal Medicinep- A case-based study. Jaypee Brothers Medical Publications; 2021. p. 285–90.
17. Prashanth LK, Sinha S, Taly AB, et al. Spectrum of epilepsy in Wilson's disease with electroencephalographic, MR imaging and pathological correlates. J Neurol Sci. 2010;291(1–2):44–50.
18 Pestana Knight EM, Gilman S, Selwa LL. Status epilepticus in Wilson's disease. Epileptic Disord. 2009;11(2):138–4319.
19. Wadia NH. An Introduction to Neurology in India. In: Spillane JD editor. Tropical Neurology. Oxford University Press London 1973;25–36.
20. Bhattacharyya KB, Basu S, Chakravarty A. Three cases of Wilson's disease masquerading as childhood muscular dystrophy. Basal Ganglia. 2012;2:115–7.
21. EASL Clinical Practice Guidelines. Wilson's disease. J Hepatol. 2012;56:671–85.
22. Roberts EA. Schilsky ML Diagnosis and treatment of Wilson disease: An update. Hepatology. 2008;47:2089–111.
23. Tümer Z, Møller LB. Menkes disease. Eur J Hum Genet. 2010;18:511–8.
24. Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet. 1993;5:327–37.
25. Bindu S, Chiplunkar S[2], Vandana VP, Nagappa M, Govindaraj P, Taly AB, et al. Huppke-Brendel Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; (1993–2019); 13
26. Alsaif HS, Alkuraya FS.2024 Nov 14. IDEDNIK (MEDNIK) Syndrome In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; (1993–2024).
27. Kono S. Aceruloplasminemia: an update. Int Rev Neurobiol. 2013;110:125–51.
28. Ogimoto M, Anzai K, Takenoshita H, et al. Criteria for early identification of aceruloplasminemia. Intern Med. 2011;50:1415–8.
29. Ferenci P. Regional distribution of mutations of the ATP7B gene in patients with Wilson disease: impact on genetic testing. Hum Genet. 2006;120:151–9.
30. Sticovaa E, Neroldovaa M, Kotalovae R, SubhanovadI A, Jirsa M. ABCB4 disease mimicking morbus Wilson: A potential diagnostic pitfall. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2020;164(1):121–5.
31. Taksande A, Parihar PH, Tayade A, Vilhekar KY. MR Imaging of The Wilson's Disease. JKScience. 2009;11:150–1.
32. Prashanth LK, Sinha S, Taly AB, Vasudev MK. Do MRI features distinguish Wilson's disease from other early onset extrapyramidal disorders? An analysis of 100 cases. Mov Disord. 2010;25(6):672–8.
33. Brewer GJ, Terry CA, Aisen AM, et al. Worsening of neurological syndrome in patients with Wilson's disease with initial penicillamine therapy. Arch Neurol. 1987;44:490–3.
34. Brewer GJ, Turkay A, et al. Development of neurological symptoms in a patient with asymptomatic Wilson's disease treated with penicillamine. Arch Neurol. 1994;51:304–5.
35. Brewer GJ, Dick RD, et al. Initial therapy of patients with tetrahydromolybdate. Arch Neurol. 1991;48:42–7.
36. Hill GHM, Brewer GJ, Prasad AS, et al. Treatment of Wilson's disease with Zinc! Oral zinc regimen. Hepatology. 1987;7:522–8.