Epidemiology, Evaluation and Management of Wilson Disease: Review Article

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ABSTRACT

Wilson disease (hepatolenticular degeneration) is a rare autosomal recessive ailment characterized by aberrant copper buildup in the body, with the brain, liver, and cornea being notably affected. Wilson illness is caused by a mutation in the ATP7B gene on chromosome 13, which regulates the protein transporter that excretes excess copper into the bile and out of the body. So far, over 500 mutations have been discovered. The most common treatment for WD is D-penicillamine (D-PCA). Patients with severe spasms, deformities, or dysphonia, as well as those who are allergic to D-PCA, should avoid it. Early Diagnosis is a key factor in saving patient’s live, and thus proper investigation should be done as soon as possible. Family screening is a must when a patient is
diagnosed to rule out any other patients in the family with the disease and because of the strong genetic factor impacting the disease. Early detection is critical for initiating therapy in the early, asymptomatic stages of the disease, rather than when liver decompensation or extensive neurological irreversible harm has already occurred. In this circumstance, the optimum technique is to finish copper investigations in the index patient's first- and second-degree relatives. In the present article we'll be discussing disease prevalence, etiology and more importantly diagnosis and management.

**Keywords:** Wilson disease; EPS; D-penicillamine; Wilson illness

### 1. INTRODUCTION

Wilson disease (hepatolenticular degeneration) is a rare autosomal recessive Disorder characterized by aberrant copper buildup in the body, with the brain, liver, and cornea being notably affected. It affects one out of every 30,000 people and can cause weakness, stomach discomfort, jaundice, personality changes, seizures, and other symptoms [1].

Wilson's illness is characterised by hepatic and extrapyramidal movement abnormalities (EPS), which express itself in a variety of ways between the ages of 5 and 45. Early diagnosis is typically difficult due to this diversity. A categorization helps to characterise current clinical data and make an early preliminary diagnosis by defining several clinical forms of Wilson's illness. Differential diagnoses must be considered until unambiguous confirmation of an autosomal recessive disease of the hepatic copper transporter ATP7B has been ruled out. Laboratory-chemical characteristics of copper metabolism can be departures from the norm unrelated to Wilson's illness, as well as other copper metabolism problems [2].

The brain and liver are generally involved in the symptoms. Tremors, muscular stiffness, difficulty speaking, personality changes, anxiety, and auditory or visual hallucinations are examples of brain or neurological symptoms. Vomiting, weakness, ascites, swelling of the legs, yellowish skin, and itching are all indications of a swollen liver. Wilson was the first to discover WD in 1912. ATP7B gene is found on the long arm of chromosome 13 (13q14-21). This gene, codes for a P-type ATPase involved in ceruloplasmin production and copper excretion. Pathogenic mutations in ATP7B impair the normal structure or function of enzymes, causing copper accumulation in various organs and resulting in a variety of clinical symptoms. Excess copper is also discharged into the bloodstream, resulting in secondary pathological buildup in other tissues, notably the brain, which can cause neurological symptoms and mental disorders. Symptoms can range from mild to severe, with the majority of cases occurring between the ages of 5 and 35. Misdiagnosis is widespread due to the disease's many symptoms. Many scientists have tried to figure out how the genotype and phenotype of WD are related. Dong et al. discovered 58 novel mutations and created the first Chinese ATP7B pathogenic mutation spectrum between 2004 and 2015 [3-9].

The first two instances of WD in China were reported by Cheng. After the 1950s, WD research exploded, and the number of documented cases progressively caught up to those of Western nations. On chromosome 13q14-21, the gene that causes WD is found. This gene, ATP7B, codes for a P-type ATPase involved in ceruloplasmin production and copper excretion. Pathogenic mutations in ATP7B impair the normal structure or function of enzymes, causing copper accumulation in various organs and resulting in a variety of clinical symptoms. Excess copper is also discharged into the bloodstream, resulting in secondary pathological buildup in other tissues, notably the brain, which can cause neurological symptoms and mental disorders. Symptoms can range from mild to severe, with the majority of cases occurring between the ages of 5 and 35. Misdiagnosis is widespread due to the disease's many symptoms. Many scientists have tried to figure out how the genotype and phenotype of WD are related. Dong et al. discovered 58 novel mutations and created the first Chinese ATP7B pathogenic mutation spectrum between 2004 and 2015 [3-9].

The majority of Wilson disease patients develop liver impairment in their first ten years of life. In the third/fourth decade of life, neuropsychiatric symptoms appear. Wilson illness is uncommon, yet it is lethal if not diagnosed and treated [1].

WD is uncommon, with an incidence of clinical illness estimated to be 1 in 30,000; however, new molecular investigations have found a higher prevalence of genetic WD (based on two alleles with harmful mutations). WD is one of just a few hereditary illnesses that may be effectively controlled if detected early and treated appropriately; nonetheless, WD is always deadly if left untreated [10].

The mean interval between the onset of symptoms and diagnosis in a German cohort of 137 symptomatic WD patients identified between
1957 and 2005 was 25.3 months. 60.3 percent of patients were diagnosed within one year, 68.2 percent within two years, and 22.5 percent of all patients were detected three years after the onset of symptoms. Neurological presentation is linked to a considerably longer period from beginning of symptoms to diagnosis than hepatic presentation in all WD groups, spanning from 2.5 to 6 years. Despite current medical developments, there appears to have been little progress in the recent few decades in terms of diagnostic time [11].

The most common treatment for WD is D-penicillamine (D-PCA). Patients with severe spasms, deformities, or dysphonia, as well as those who are allergic to D-PCA, should avoid it. In China, dimercaptosuccinic acid (DMSA) was the first medicine used to treat WD. For individuals with significant neurological symptoms, DMSA is indicated as an alternative. Monozygous treatment is also appropriate for asymptomatic WD, as well as maintenance therapy when copper chelating drugs have been used. Because WD is a hereditary illness that may be treated, the majority of individuals have a good prognosis. Although the frequency of WD in China is higher than in Western nations, clinical studies are scarce in China, and therapy is frequently relied on expert opinion and data from other countries. As a result, specialized therapies for Chinese patients with WD must be researched and provided [3,12-14].

2. ETIOLOGY AND PATHOPHYSIOLOGY

Wilson illness is caused by a mutation in the ATP7B gene on chromosome 13, which regulates the protein transporter that excretes excess copper into the bile and out of the body. The protein transporter is found in the liver and brain’s trans-Golgi network. Copper is excreted mostly (95 percent) through the liver. Excess copper builds up in the liver, then leaks into the bloodstream, eventually affecting other organ systems. Excess copper induces the production of free radicals, which cause the oxidation of essential proteins and lipids. The mitochondria, nuclei, and peroxisomes are the first to alter [1].

The ATP7B gene has 20 introns and 21 exons and is found on the short arm of chromosome 13. According to The Human Gene Mutation Database, more than 700 mutations have been identified, and individuals might be homozygous for one disease-causing mutation or compound heterozygous for two separate disease-causing mutations. Nearly all 21 exons can be affected by mutations, which are typically missense and nonsense. Exon 14 missense mutation H1069Q is quite prevalent. About 50–80 percent of WD patients from Central, Eastern, and Northern Europe had the H1069Q mutation on at least one allele [10].

The ATP7B mutation causes the ATPase to be missing or non-functional, resulting in impaired ceruloplasmin production and biliary copper excretion. Copper toxicity occurs as a result of copper buildup in hepatic and extrahepatic tissues, leading in a variety of clinical manifestations of Wilson disease. Copper, as a prooxidant, produces enough reactive oxygen species to cause cellular damage. A conformational shift in the antiapoptotic protein, X linked inhibitor of apoptosis, causes copper to cause apoptosis (XIAP) [15]. Other proteins and altered genes beyond ATP7B have been investigated as possible contributors to the WD phenotype. PNPLA3, or patatin-like phospholipase domain-containing protein 3, is involved in triglyceride metabolism; a PNPLA3 variation linked to non-alcoholic fatty liver disease (NAFLD) has also been linked to the degree of hepatic steatosis in WD24 patients. PNPLA3 deficiency has been associated to triglyceride buildup in hepatocytes and stellate cells. Furthermore, the ApoE ε4 allele of the apolipoprotein E gene (ApoE), which is involved in lipid metabolism and neurodegenerative illnesses, was thought to be a modulator of the WD phenotype, however a comprehensive investigation found no link between the ApoE ε4 genotype and the hepatic or neurological phenotype in WD. ApoE 4-positive women, on the other hand, had illness start at a younger age than women with the ε3/ε3 genotype, especially if they were also homozygous for the H1069Q mutation. Copper buildup in Bedlington terriers is caused by mutations in the copper metabolism domain containing 1 (COMMD1) gene (previously MURR1), and one research found COMMD1 variations in 30 percent of 63 individuals [10].

3. EPIDEMIOLOGY

With a gene frequency of 0.56 percent, the prevalence of WD, a rare illness, is comparable in most world locations, equal to around 0.5 cases per 100000 population, or the most frequent number 30 cases per million. Nonetheless, the condition is far less prevalent in
other areas/countries, with specific mutations being reported more commonly in some groups. So far, over 500 mutations have been discovered, and the lower number of clinically evident instances compared to the frequency of allele carriers in the population likely reflects the mutations' lesser penetrance [16-20].

This illness affects 1 in every 30,000 people, with 1 in every 90 people being a carrier. Wilson illness is more common in some groups due to a higher percentage of consanguinous marriages. Males and females are both impacted in the same way. The typical age of onset is four to forty years old, however this illness has been found in infants as young as three and individuals as old as seventy [1].

In 1968, Sternlieb and Scheinberg estimated the prevalence of WD to be 5/1,000,000. Bachman et al. researched WD in Leipzig, Germany, from 1949 to 1977, and found that the frequency of WD was 29/1,000,000 births. According to Saito, the frequency of WD was 33/1,000,000 newborns in 1981. In 1991, Park et al. used computerised hospital data, survey findings, and death certificates to try to figure out how common WD was in Scotland. In a population of 5,090,700 people, they found 21 cases with WD, resulting in a prevalence of 4/1,000,000. Reilly et al. utilised a similar methodology to evaluate the prevalence of WD in the Republic of Ireland in 1993, and they found 26 cases during a 19-year period. In five of the cases, patients died before receiving a definitive diagnosis. The adjusted birth rate of people with WD was 17/1,000,000 between 1950 and 1969, corresponding to a gene frequency of 0.41 percent and an incidence of heterozygotes of 0.82 percent. To obtain a minimal illness estimate, the gene frequency was updated to 0.36 percent and the incidence of heterozygotes was modified to 0.72 percent to account for the greatest degree of kinship [3,21-26].

So far, over 500 mutations have been discovered, and the lower number of clinically evident instances compared to the frequency of allele carriers in the population likely reflects the mutations' lesser penetrance. In Europe and North America, the most prevalent mutations are His1069Glu (H1069Q), Arg778Leu in South Korea, Japan, and China, 2007del in Iceland, and Met645Arg in Spain. The illness is most common in Germany (2.5/100000 people), Japan (3.3/100000 people), and Austria (3.0/100000 people). Costa Rica, on the other hand, has the highest incidence rate in the world (4.9/100000 people). The most common mutation is Asn1270 Ser, which was previously exclusively seen in Sicilian, Lebanese, and Turkish populations, probably due to increased consanguinity and a potential founder effect. The second place with a high prevalence (estimated 1/10000-1/7000) is Sardinia, where a well-documented founder mutation (-441/-427del) is widely frequent (67%) and all other mutations have a relative frequency below 10% [3,27-40].

Presymptomatic WD patients who comply with therapy have mortality rates that are equivalent to the general population. However, studies demonstrate that death rates in patients with WD (5–6.1%) are greater than healthy controls in the total WD group (independent of adherence, clinical symptoms, beginning stage of illness, or type of therapy). Survival is impacted by severe hepatic and neurological illness, as well as nonadherence to therapy [10].

4. EVALUATION

Wilson illness must be diagnosed and treated as soon as possible if it is to be fully recovered. Otherwise, the condition is deadly. As a result, any unexplained hepatic or neurological manifestation should be considered.

Molecular diagnostics (laboratory diagnosis), diagnostic imaging, and genetic analysis are all used to diagnose WD. The use of molecular diagnostics has risen. Liver illness, brain and nerve system damage, osteoporosis, and K-F rings are all clinical symptoms of WD. It's possible that liver damage will go undetected. Routine liver function tests do not provide diagnostic information. Tremors can help doctors diagnose WD that affects the neurological system. Patients with neurological or mental symptoms are more likely to be diagnosed with WD. The existence of K-F rings near the cornea's edge can also be used to diagnose the condition [3].

A ceruloplasmin level test can be ordered if you have a strong suspicion of Wilson illness is present. It will be below 20 mg/dL (normal range is 20 to 40 mg/dL). Copper levels in the urine will be increased by more than 100 mcg/dL. These two lab results with Kayser-Fleischer rings are generally adequate to diagnose Wilson disease, but if another diagnosis is possible, schedule a liver biopsy to check for liver copper levels; this is
the most accurate test for Wilson disease. Any protein deficient condition can cause low amounts of ceruloplasmin. A copper level more than 250 mcg/g of dry liver tissue indicates a good outcome. The use of an MRI to screen for brain involvement is beneficial. Elevated AST and ALT levels cause liver function tests to be abnormal [1].

Hepatic symptoms are the most common onset presentation in children, with an average age of 11 years. However, there are some examples of liver disease caused by WD in very young patients, including three young children aged 8, 9, and 13 months who were evaluated for transaminitis, a 3-year-old with cirrhosis, and a 5-year-old with acute liver failure (ALF). In large case series, the average age of commencement of neurologic symptoms is about 15–21 years old, a decade after the onset of liver disease, however a few patients have been identified with an initial neurologic onset before the age of 10. Late-onset WD in people over 40 is also recorded in the literature, with 94 examples published so far: 20 case reports, four case series (28 patients), and one big European research of 46 patients [11].

In one-third of patients, psychiatric symptoms appear before neurological or hepatic symptoms. In youth, poor academic performance or personality abnormalities such as impulsivity, labile mood, sexual exhibitionism, and inappropriate conduct might be observed, but older patients may display psychotic symptoms such as paranoia, schizophrenia, or sadness. In a group of Wilson disease patients from Bangalore, affective disorder, significant depression, and dysthymia were the most prevalent psychiatric diagnoses [15].

The basal ganglia were the most commonly damaged regions on nuclear magnetic resonance imaging (MRI) of the brains of patients with WD. The caudate nucleus, thalamus, midbrain, pons, and cerebellum show hypointensity on T1-weighted imaging and hyperintensity on T2-weighted scans, but hyperintensity on T1-weighted images and hypointensity on T2-weighted images can occur in select rare situations. The basal ganglia, thalamus, and brainstem are more likely to experience simultaneous signal alterations. Patients with WD exhibit different degrees of frontal brain atrophy, ventricular enlargement, and hydrocephalus. Because the brain abnormalities observed on MRI might disappear after successful therapy, MRI is a helpful tool for monitoring treatment efficacy [3].

Wilson’s illness must be investigated in differential diagnosis for the existence of unclear symptoms related with the basal ganglia and cerebellum, especially before the age of 45, and in unusual cases even beyond that. Knowing how Wilson’s illness progresses clinically (clinical variations) aids in spotting differences in clinical findings.

Atypical liver features at diagnosis: Asymptomatic hepatomegaly, isolated splenomegaly, persistent or intermittent elevations of serum aminotransferases, jaundice, fatty liver or pseudo-autoimmune hepatitis, acute hepatitis, compensated or decompensated cirrhosis, and ALF are some of the hepatic symptoms of WD at presentation. Some liver disease symptoms, particularly those that resemble non-alcoholic steatohepatitis (NASH) in obese people or ALF, might be deceiving [11].

Wilson illness should be considered if symptoms suggestive of the condition are present, or if a family member has been diagnosed with it. Most exhibited slightly elevated aspartate transaminase, alanine transaminase, and bilirubin levels, as well as mildly abnormal liver function tests. Because injured liver cells are unable to make albumin, the prothrombin time is extended; similarly, the prothrombin time is prolonged because the liver is unable to create proteins known as clotting factors. Wilson-related acute liver failure patients had decreased alkaline phosphatase levels. If there are neurological symptoms, a T2 sequence MRI of the brain may reveal hyperintensities in the basal ganglia. The unique "face of the gigantic panda" pattern may be visible on MRI [1].

Because the serum Cp level may be normal in ALF related to WD, and 24-hour urine copper is generally high in all ALF patients regardless of the aetiology, diagnosing WD in the setting of ALF remains difficult. Hemolytic anaemia, which is frequent in ALF owing to WD, should be a warning signal. Because AST is present in red blood cells, this results in a disproportionate rise of AST relative to ALT, and an AST/ALT ratio of >2.2 has a sensitivity of 94 percent and a specificity of 86 percent for the diagnosis of WD [15].

KFR: Copper deposition in the Descemet's membrane of the cornea is macroscopically
evident as the KFR. They were first characterised in 1902 by Kayser, ten years before Wilson's discovery of progressive lenticular degeneration. They show as a brown ring on the cornea's edge that isn't always closed. They are considered a cardinal symptom. Nonetheless, KFR are among the early signs of the disease in children, yet they are frequently absent in the early stages of the disease. KFR was only found in 44–62 percent of individuals with Wilson's disease who had hepatic symptoms, and they were almost never seen in children with liver illness. Furthermore, they are more prevalent in patients with the homozygous H1069Q mutation at the time of diagnosis than in individuals with the compound heterozygous H1069Q mutation [2].

Genetic testing has also become commonplace. Mutations in the ATP7B gene are the cause of WD. Direct sequencing analysis is currently the most accurate method of detecting ATP7B mutations. Point mutations are the most prevalent changes, although other types of mutations, such as minor deletions or insertions, entire deletions, and splice site alterations, have also been discovered. Previous research has suggested that WD in China is caused by a combination of common and unusual mutations [3].

Family screening is recommended because early detection is critical for initiating therapy in the early, asymptomatic stages of the disease, rather than when liver decompensation or extensive neurological irreversible harm has already occurred. In this circumstance, the optimum technique is to finish copper investigations in the index patient's first- and second-degree relatives.

5. TREATMENT

Treatment should preferably begin soon after diagnosis in pre-symptomatic patients (where testing is done as part of a screening for afflicted family members) or immediately following rapid diagnosis in symptomatic people. If therapy is started early enough, deterioration can be avoided, and life expectancy can be equivalent to that of those who do not have the condition. Patients with WD have a good prognosis if they stick to their treatment regimen. On the contrary, the disease's natural course is nearly often marked by gradual, unrelenting deterioration, eventually leading to death from liver or brain disease. Discontinuing medication can be fatal, putting the patient at risk of FW and increasing mortality, as shown in a research in which 8 of 11 patients who stopped receiving treatment died on average 2.6 years later [16].

D-penicillamine (chelator): D-penicillamine has been used as a first-line therapy for Wilson disease since the 1950s. It is taken as tablets two or three times a day. Pyridoxine and D-penicillamine must be administered together. To confirm chelation and enhanced copper excretion, 24-hour urine copper excretion is employed. Urinary copper levels should be five to 10 times normal; if they're lower, noncompliance may be a problem, or body copper reserves may have been depleted sufficiently [41].

- During D-penicillamine treatment, a complete blood count and urinalysis must be checked on a regular basis. Serious adverse effects, such as severe thrombocytopenia, leukopenia, aplastic anaemia, proteinuria, nephrotic syndrome, polyserositis, Goodpasture syndrome, and severe skin reactions, can occur in up to 30% of people. It's possible that an allergic reaction with fever, rash, and proteinuria will occur early on. If any of these adverse effects are discovered, D-penicillamine should be stopped and replaced with another medicine. If no other options are available, D-penicillamine-induced side effects may be managed with steroid co-administration.
- D-penicillamine is an immunosuppressant that inhibits collagen cross-linking. Individuals may develop atypical skin and connective tissue collagen after decades of therapy, as well as prolonged depletion of copper (and potentially) other trace metals.
- In the absence of proper clinical evaluation of this therapy approach, D-penicillamine should not be administered in conjunction with zinc.

Trientine (chelator): When D-penicillamine is not tolerated, trientine, also known as triethylenetetramine dihydrochloride (2,2,2-tetramine) or trien, is used as a second-line therapy. Because of its efficacy and superior tolerance than D-penicillamine, it is becoming more widely accepted as a first-line treatment; nonetheless, it is not yet widely accessible in all countries [41].

- All trientine patients should have their complete blood count and urine checked on a regular basis.
- Gastritis with nausea is a rare adverse effect, as is iron deficiency anaemia in situations of overtreatment.
- Trientine should not be used in conjunction with zinc until a thorough evaluation of the combination has been completed. According to recent findings, a combination of trientine and zinc, given at different times during the day such that each treatment is given 5-6 hours apart, may be beneficial in severely decompensated hepatic Wilson disease.

**Ammonium TTM:** Is a chelating medication having anti-angiogenic characteristics that was first used in veterinary therapy to treat copper intoxication. When taken after meals, ammonium TTM binds to the copper in the food, preventing it from being absorbed. It is absorbed into the bloodstream and creates a complex with circulating copper, limiting cellular absorption and resulting in urine excretion if taken on an empty stomach. The recommended dosage is 20 mg three times a day with meals and 20 mg three times a day between meals. The documented negative effects of ammonium TTM include paradoxical worsening, bone marrow suppression, and hepatotoxicity due to its severe chelating properties. However, as compared to trientine, the possibility for neurological degeneration and adverse effects is said to be lower. Ammonium TTM is currently unavailable in India and many other countries. By week 24 of therapy, 57 percent of patients had improved liver function tests and 72 percent had improved free copper levels, according to ongoing phase-2 multicenter studies using a more stable version of a copper chelator (bischoline TTM [WTX101]). More information on the usage of this medication in the treatment of diverse phenotypes of WD is required [42].

**Hepatic WD treatment via liver transplantation:** Durand et al. reported in 2001 that for the great majority of patients (90 percent) presenting with fulminant WD without hepatic encephalopathy (HE) upon admission, early use of DP might prevent LT. Nazer's score (serum bilirubin, international normalised ratio (INR), and serum albumin) was renamed New Wilson’s Index in 2006 when two more parameters (AST and white blood cell count) were added to the score (NWI). Nonsurvivable without liver transplantation was linked to a NWI score of less than 11. NWI and Pediatric End-Stage Liver Disease/Model for End-Stage Liver Disease were shown to have modest accuracy in predicting outcomes in WD in a research from South India. The authors used regression analysis to create a model that used hepatic encephalopathy and bilirubin to predict the prognosis in a fulminant WD presentation. Fischer et colleagues found three of the six patients with NWI scores that predicted mortality, and two of these three patients lived without a transplant. They warned that the results might not be reliable and that this subgroup needed more research [42-45].

**6. CONCLUSION**

There’s no doubt that Wilson disease is one of the most concerning clinical challenges that may face the health care system, the challenge of the disease involves around the asymptomatic nature of it, so most patients being diagnosed into later stages of the disease when already great damage has been occurred, and thus the key to effective treatment is early diagnosis. Family screening of Wilson disease's patient is a must specially to first- and second-degree relatives, because there a high chance of existence of another genetic carriers in the family due to he genetic etiological nature of the disease. With that being said we hope in the future of existence of more effective evaluation and treatment options.

**CONSENT**

It is not applicable.

**ETHICAL APPROVAL**

It is not applicable.

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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