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Review Article

A Detail Insight of Wilson's Disease and its Treatment

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Abstract

Wilson disease is a rare inherited autosomal recessive genetic disorder caused by abnormal copper accumulation in the body, particularly involving the brain, liver, eyes, and other vital organs. This is also known as hepatolenticular degeneration. It primarily affects the liver and basal ganglia of the brain, but it can affect other vital organs too. It results from a mutation in the gene encoding the Wilson disease protein (ATP7B). It results from a mutation in the gene encoding the Wilson disease protein (ATP7B). A healthy body excretes extra copper through urine after the liver filters it out. Wilson's disease prevents the liver from effectively removing the excess copper. The extra copper then builds up in organs such as the brain, liver, and eyes; which is the reason why symptoms are usually related to the brain and liver. One of the 23 chromosomes in humans, chromosome 13, has a gene that causes Wilson's disease. For six months, a 12-year-old kid with Wilson's disease complained of speech problems, swallowing issues, and general stiffness. About 97 percent of those with Wilson's illness have K-F rings. Vomiting, weakness, ascites, yellowing of the skin, and brain or neurological symptoms like tremors, muscle stiffness, difficulty speaking, personality changes, or visual hallucinations are only a few of the symptoms associated with the liver. Sunflower cataracts are visible in 1 in 5 patients with Wilson's illness. One in 90 people in the general population are carriers of Wilson's illness. A liver biopsy, clinical evaluation, blood testing, urine tests, and a challenging diagnosis are all required. The family members of persons with the condition may be screened via genetic testing. For Wilson's disease to be stopped in its tracks, early detection is essential. Treatment can be done by both ayurvedic remedies using herbs and allopathy using drugs with specific target sites important for managing Wilson disease. WD can be treated with Copper chelating agents and Herbs act as a supporting treatment. Some drugs are still in the clinical trial phase.

Keywords: Kayser-Fleischer rings, Wilson disease (WD), ALXN1840, d-Penicillinase, Vatavyadhi.

INTRODUCTION:

Wilson disease (WD), which was always deadly, was first identified by Dr. Samuel Alexander Kinnier Wilson in 1912 as a novel illness of familial lentiform degeneration with liver cirrhosis. A hereditary condition affecting copper metabolism is known as Wilson's disease (WD). Transmembrane Copper-Transporting ATPase 2 (commonly known as ATP7B), which mediates the removal of copper from the bile and delivers copper for the functional synthesis of ceruloplasmin (the major copper-transporting protein within the blood), is the gene responsible for the disease. Homozygous or compound heterozygous mutations (the presence of two different mutant alleles) in ATP7B are the cause of the disease ¹. For women with WD, it's crucial to be informed about pregnancy outcomes, the use of anti-copper treatment during pregnancy and breastfeeding and the possibility that treatment may have teratogenic effects because WD is typically diagnosed in young adults, including women who are capable of having children ². It is uncommon to have WD and pregnancy because the condition can cause infertility and recurrent abortions. Uncertainty exists on the exact cause³. In order to prevent the liver illness from getting worse or the development or exacerbation of neurological symptoms, it is crucial that individuals with Wilson disease who are pregnant maintain their medication. Choose treatments that have the lowest risk of fetal problems, but promote and enhance fetal growth and

development, in order to protect the fetus⁴. The ATP7B gene, which produces a transmembrane copper-transporting ATPase which regulates the expulsion of copper into bile and provides copper for the effective synthesis of ceruloplasmin, is the source of the homozygous or compound heterozygous variations that cause the disease. (The major copper-containing protein in the blood) Hepatocytes become overloaded with copper in WD, which is related with liver disease. In addition to being discharged into the bloodstream, excess copper can accumulate pathologically in other tissues, most notably the brain, which can cause neurological symptoms and behavioural disorders. The majority of the time, between the ages of 5 and 35, symptoms appear⁵. As WD is one of the rare curable neurogenetic illnesses, patients should start therapy right away as they are diagnosed. D-penicillamine, dimercaptosuccinic acid (DMSA) trientine, and sodium dimercaptosuccinate (DMPS) are the most utilized copper chelation medicines^{6,7}. By decreasing copper absorption, zinc reagents efficiently treat WD; they are typically used as maintenance therapies and have little negative effects⁸. However, it soon became clear that dimercaprol was not a viable long-term therapy choice due to its high incidence of side effects, the rapid development of drug tolerance, and diminishing clinical advantages. The prognosis for WD was altered by John Walshe's introduction of penicillamine in 1955, which made survival as well as a

dramatic and prolonged clinical recovery possible. After the development of additional efficient medical therapies for patients with life-threatening liver failure or those who had trouble tolerating medical treatment, liver transplantation became an alternative⁹. The use of liver transplantation (LT) to treat neurological symptoms in WD is not advised by international recommendations on the condition's management¹⁰. The patient received oral medication along with Ayurvedic treatments like Abhyanga, Swedana, Basti, and Nasya. After two treatments, the patient saw symptomatic improvement in their clinical characteristics. In light of this, it can be said that internal Ayurvedic medicine and the Panchkarma treatment can help patients with chronic diseases enhance their quality of life (QOL)¹¹. *Ahar* like chocolate are completely forbidden since they contain excessive amounts of copper. Other foods with high copper content include nuts and oilseeds, condiments, and spices. Amla, Ridge gourd, Pumpkin, Mango green, French beans, Drumstick, Cluster, Cabbage, Dry Mango, and Drumstick leaves are only a few of the foods that contain copper in small amounts. To prevent and treat Wilson's disease more effectively, one should adhere to this *pathya* (diet)¹². In this article, we review the current understanding of WD, including epidemiology, genetics, the pathophysiology of the disease, clinical signs and symptoms, and diagnosis. We also discuss current management options as well as potential future medical remedies from Ayurveda that tackle the fundamental cause of the increased copper accumulation in WD.

EPIDEMIOLOGY:

Epidemiological studies from the 1970s showed that Japan had 33 instances per 1,000,000 people and that there were 29 cases of WD per 1,000,000 people in Germany¹³. Due to more accurate diagnostic knowledge, the stated crude prevalence of Wilson illness fluctuates and has risen over time. 1:40,000–1:60,000, according to recent major research¹⁴. In non-isolated groups, the global prevalence of WD was estimated in 1984 to be 1 case every 30,000 people, with an altered carrier rate (individuals with one disease-associated allele) of 1 in 90 people (corresponding to just under 1% of the overall population)¹⁵. The high rates of proximity in the remote area were probably to blame for the increased occurrence. Additionally, a research using information from a substantial French cohort discovered that roughly 1 in 31 people are heterozygous carriers¹⁶, and this is in line with the predicted disorder rate of one case per 1000 live births. However, more research on illness-specific mutations is required. Wilson disease with inadequate penetration is indicated by the difference between the heterozygous frequency of carriers and the reported prevalence¹⁷. According to some research, Wilson disease affects both men and women equally, although women are more susceptible than men to get acute liver failure as a result of Wilson illness. Even so, a significant registry analysis of 627 Wilson disease patients indicated a

small male predominance. (52 percent). Male patients were more likely than female patients to have neuropsychiatric disease at the time of diagnosis (75 versus 58 percent) and were less likely to have hepatic disease. (25 versus 41 percent)¹⁸. About 40%–50% of individuals have initial neurologic issues, and the other patients either exhibit hepatic or predominantly mental symptoms¹⁹. Around 50% of individuals with a known mutation will also have disease symptoms²⁰. WD may manifest at any age, from infancy (with increased transaminases, tested for an unknown reason) until the eighth decade. (with mild neurological clinical symptoms)²¹. WD can have a wide range of phenotypes and penetrances. There is no guarantee that patients with two mutations that cause diseases would exhibit an altered copper metabolism²².

PATHOPHYSIOLOGY:

Wilson disease is characterized by a defective copper excretory system that causes copper to build up in the liver and leak into the blood, where it begins to build up in a number of organs and tissues, such as the subthalamus, putamen, cortex, kidneys, and cornea. A toxic hydroxyl group is formed when copper levels are too high, causing oxidative stress in the cells to rise. Copper is a transition metal. The cells are harmed by this oxidative stress, which results in clinical manifestations like

- liver failure,
- behavioural issues,
- abnormalities of movement,
- The corneal Kayser-Fleischer rings.

The demand for copper in the body is mostly due to its role as a cofactor for several enzymes, including tyrosinase, ceruloplasmin, Cytochrome C Oxidase, dopamine beta-hydroxylase, and superoxide dismutase. Copper enters the body through the digestive system and is transported there by a transporter protein called copper membrane transporter, which is present in the small bowel cells. This transporter facilitates the movement of copper within cells, where some of the copper is transported by ATOX1 to an organelle known as the trans-Golgi network and some of the copper is bound to metallothionein. An enzyme known as ATP7A releases copper into the portal vein to the liver in response to growing copper levels. The CMT1 protein and metallothionein are carried by liver cells, whereafter ATOX1 binds them inside the cell. Here, ATP7B binds the copper to ceruloplasmin, releasing it into the bloodstream while secreting any surplus copper into bile. In WD, ATP7B is not performing any of its two tasks. Copper does not exist in ceruloplasmin when it is released, and as a result, it accumulates in the liver instead of being promptly broken down in the bloodstream.²³

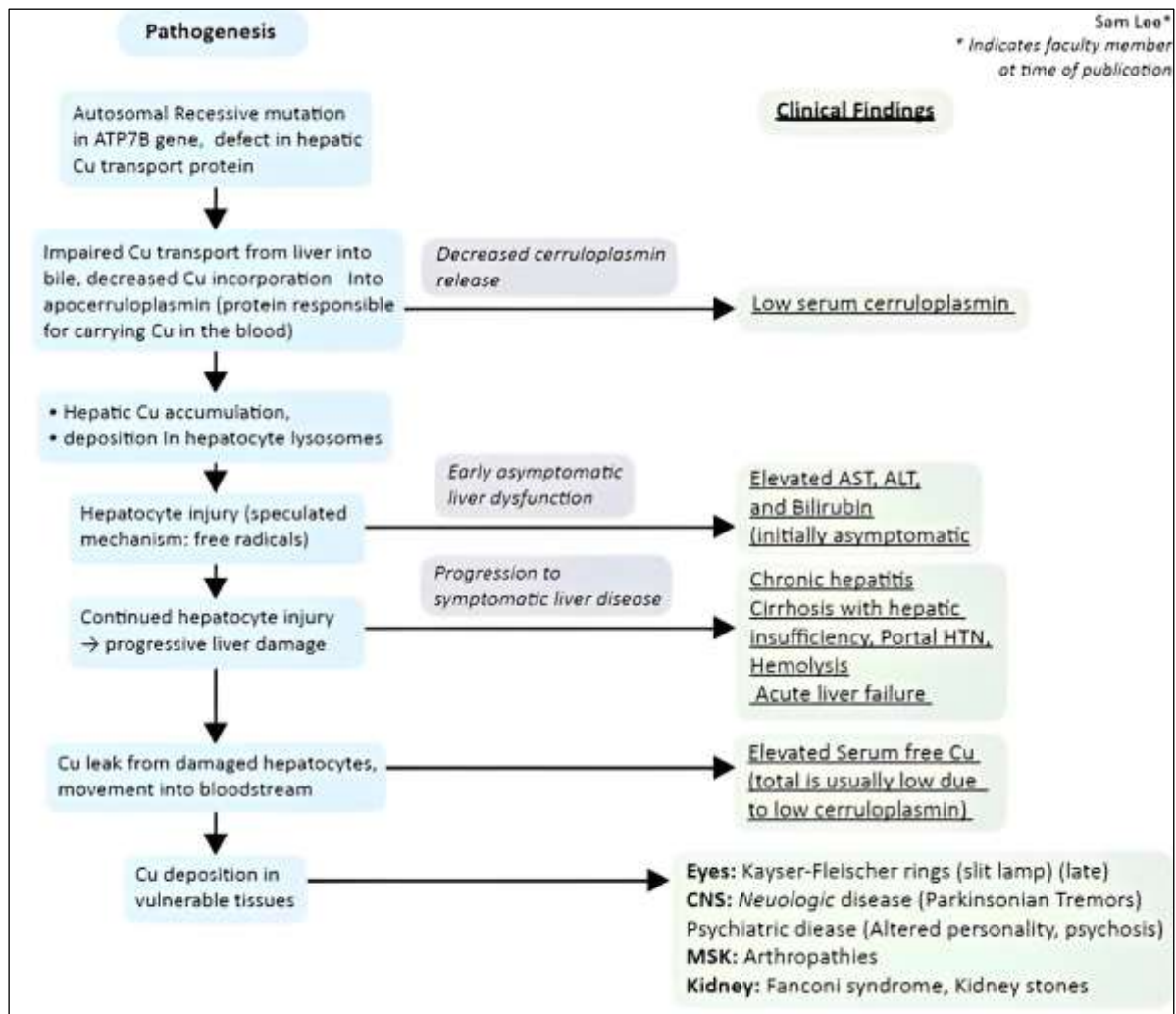


Figure 1: Wilson Disease's Pathophysiology²⁴

INHERITANCE OF WILSON'S DISEASE:

Due to the fact that Wilson disease is an autosomal recessive condition, both parents of the affected child must have at least one genetic mutation (an abnormal change in the gene) that causes WD. There is a 25% probability that each kid of two carriers may inherit two mutations that cause WD. Of all known races and ethnicities, the disease affects at least one in 30,000 persons.

Wilson disease is caused by a gene that is placed on chromosome 13, one of the 23 chromosomes in humans. The copper transport protein that is crucial for integrating copper into ceruloplasmin and expelling extra copper from the liver is made by the gene known as ATP7B. A defective copper transporter caused by gene mutations is incapable of moving

copper at all or in an efficient manner. In the liver and other organs, this extra copper builds up. Most patients with Wilson's illness have no family history of it. Carriers are people who have only one aberrant gene. Carriers (heterozygotes) may have slight but unimportant copper metabolism problems. Carriers should not be treated because they never become sick. The prevalence of Wilson disease carriers in the general population is one in 90. Patients with Wilson disease (homozygotes) do become ill and require lifelong therapy or they may eventually acquire a severe, fatal condition. Every kid of a person with Wilson disease (WD) inherits at least one faulty copy of the WD gene from their WD-affected parent, making them at least carriers of the condition²⁵.

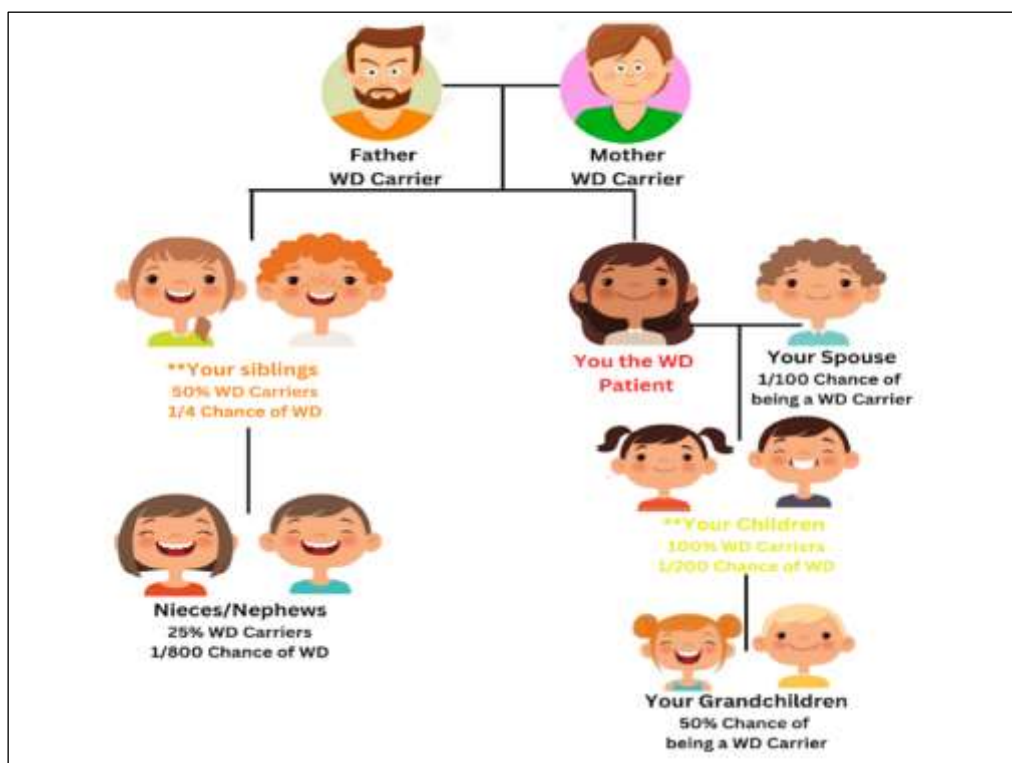


Figure 2: Pedigree of Wilson diseases ²⁵

SYMPTOMS:

Symptoms and signs involved in Wilson's disease are distinguished based on the organs involved such as the liver, brain, blood, and corneas ²⁶

1. Liver-related symptoms:

- Abdominal pain ²⁶
- Bleeding ²⁶
- Jaundice ²⁶
- Vomiting ²⁷
- Weakness ²⁷
- Ascites ²⁷
- Swelling of the legs ²⁷
- Yellowish skin ²⁷
- Itchiness ²⁷
- Bloating in the abdomen ²⁸
- Spider angiomas, or visible branch-like blood vessels on the skin ²⁸
- Muscle cramps ²⁸
- Weight loss ²⁸
- Nausea ²⁸

2. Brain or neurological symptoms:

- Tremors
- Muscle stiffness
- Trouble speaking
- Personality changes

- Anxiety ²⁷
 - Auditory or visual hallucinations ²⁷
 - Depression ²⁶
 - Other psychiatric problems ²⁶
 - Memory, speech, or vision impairment ²⁸
 - Abnormal walking ²⁸
 - Migraines
 - Drooling
 - Insomnia
 - Clumsiness with hands
 - Personality changes
 - Changes in mood
 - Problems in school
- ### 3. Blood-related symptoms:
- Red blood cell abnormalities
 - Low platelet counts. ²⁷
- ### 4. Eyes-related symptoms:
- Unusual golden-brown eye discolorations called Kaiser-Fleischer rings or black rings (a warning indication) are brought on by deposits of too much copper. About 97 percent of individuals with Wilson's illness have K-f rings.
 - In 1 in 5 patients with Wilson's illness, sunflower cataracts are visible. This has a distinctive centre that is multicoloured and spokes that extend outward. ^{27,29}



Fig. 3: Kayser-Fleischer rings³⁰

5. Other organ-related symptoms:
 - Bluish discoloration in the nails
 - Kidney stones
 - Premature osteoporosis, or lack of bone density
 - Arthritis
 - Menstrual irregularities
 - Low blood pressure

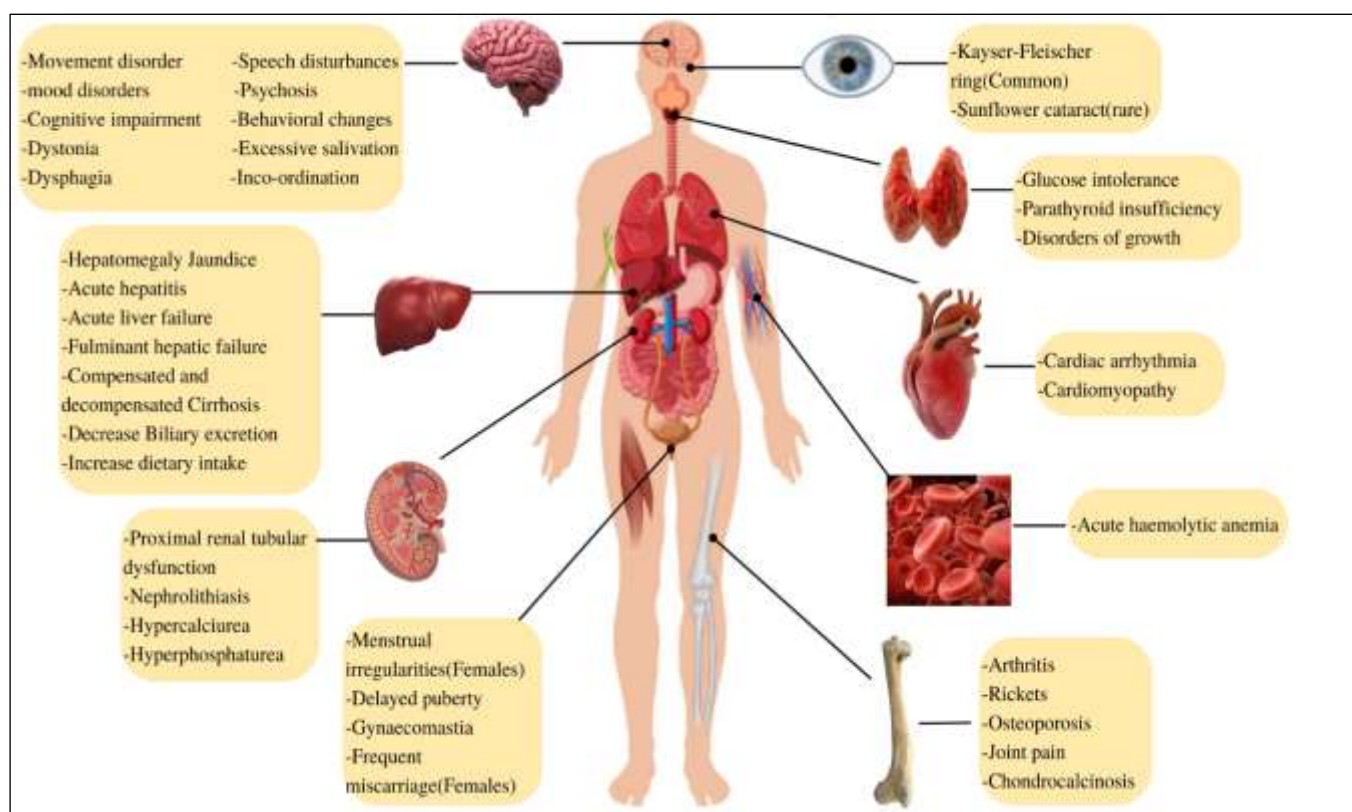


Figure 4: Symptoms of Wilson Diseases²⁶⁻³⁰

DIAGNOSIS OF WILSON DISEASE:

Wilson's disease diagnosis can be complicated and should be evaluated by a physician familiar with the various testing types and how to interpret the tests. Due to its rarity, common symptoms like psychiatric disorders or hepatitis may first be linked to other conditions. Wilson's disease is frequently asymptomatic; yet, substantial liver damage can happen even before any symptoms arise. Wilson's often does not cause noticeable symptoms until it is serious. Tests may include:

1. Blood tests-
 - To assess liver function
 - Blood counts
 - Detect ceruloplasmin levels (a copper-carrying protein that is often low in Wilson Disease)
 - Sometimes serum copper³¹
 - 24-hour urinary copper excretion³¹
2. Urine tests – to look for excess copper that is excreted in urine (24 hours of urine)
3. Eye exam –

- To look for brown or ring-shaped coloring the cornea (Kayser-Fleischer rings)
 - Slit-lamp examination for Kayser-Fleischer rings³¹
3. Imaging tests – Imaging studies may be used to look for symptoms of Wilson's disease or other diseases in the brain in patients who have symptoms related to the nervous system. Medical professionals may use:
 - Magnetic resonance imaging (MRI), which creates precise images of organs and soft tissues without the use of X-rays.
 - Computerized tomography (CT) scan, which generates images using a combination of X-rays and computer technologies.³¹
 4. Genetic testing –is very helpful when positive. Before submitting the test, one should find out whether their insurance will cover it because testing is frequently substantial.

SCREENING OF WILSON DISEASE²⁹:

- Because early treatment is most effective, screening is indicated for anyone who has a sibling, cousin, or parent with Wilson disease.

- Slit-lamp examination, assessment of transaminase levels, serum copper and ceruloplasmin levels, and 24-hour urine copper excretion are all part of the screening process.
- A liver biopsy is performed to assess the level of hepatic copper if any abnormalities are found.
- Ceruloplasmin levels are low in the first several months of life, hence infants shouldn't be tested until after age one. Children under the age of six with healthy test results ought to be retested five to ten years later.
- Investigations into genetic testing are ongoing.

STAGES OF WILSON DISEASES 27 :

- Stage 1: Accumulation of Cu within the liver initially.
- Stage 2: Sudden release of copper into the bloodstream after acute translocation of copper inside the liver.
- Stage 3: Prolonged build-up of copper in extrahepatic tissues other than the liver, such as the brain
- Stage 4: Chelation therapy is used to restore the equilibrium of copper.

CLASSIFICATION OF WILSON'S DISEASE:

As a result of several qualitative and quantitative symptoms that appear at various periods, Wilson's illness is characterized by a variety of presentations 32,34. The WD also known as Copper storage disease33.

It is important to identify the fundamentals that are shared by many patients while also considering the uniqueness of each patient.

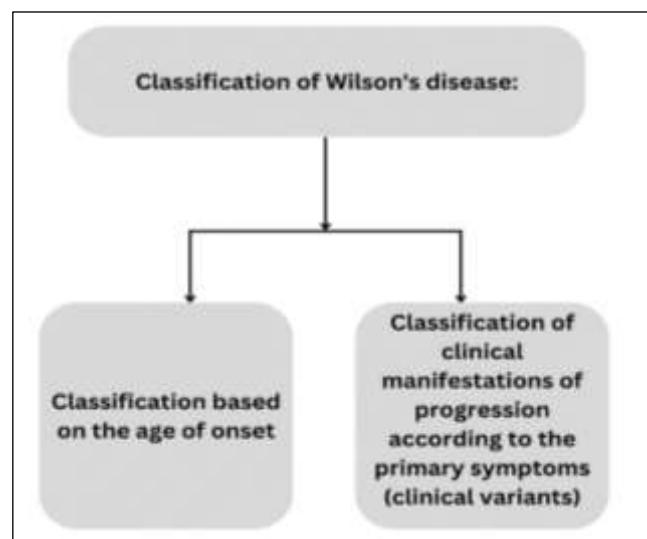


Figure 5: Classification of Wilson Diseases³⁴

1. Classification based on the age of onset

Most of symptoms up until adolescence are gastrointestinal with hepatic or haemolytic findings 34,35. Therefore, vaguely elevated transaminases and bilirubin, icteric flare-ups, symptoms of virus-negative acute hepatitis, and hepatosplenomegaly should raise suspicion. Acute liver failure is also possible. Haematologically, the occurrence of Coombs-negative haemolysis and unclear anemia leukopenia, and thrombocytopenia are suspicious.

Central nervous system symptoms with dysarthric, extrapyramidal, and mental manifestations start to occur after puberty without having an exact age limit and after overcoming unnoticed bland gastrointestinal abnormalities.

Changes in the sonographic liver texture, a Kayser-Fleischer ring (KFR), transaminases, production parameters, albumin and coagulation factors, cholinesterase, and ammonia might all support the supposition34.

2. Classification of clinical manifestations of progression according to the primary symptoms (clinical variants)

The most exact classification was likely offered by Konovalov in his 1960 monograph on the basis of clinical and pathological-anatomical occurrences. After that, five clinical variants were identified (Fig 6), each of which was adjusted based on clinical characteristics according to Lössner et al. 1980 and Bachmann et al. 1988.

A dystonic form and a choreatic version of the mixed type are also distinctions made by some authors34. Psychological symptoms can also vary and might include schizophrenia, depression, personality abnormalities, and behavioural issues that lead to criminal behaviour. Instead of being correlated with the presence of hepatic symptoms, they are more so with the onset of neurological symptoms36. Psychiatric symptoms accompany Wilson's illness in over 10% of cases. Wilson's disease can also present exclusively psychiatrically, according to published literature.

According to extrapyramidal symptoms, cognitive impairment, and mental illnesses, Oder et al. [1993] suggest subdividing the neurological form of progression into three groups for this reason 36. On the other hand, the (pragmatic simple) categorization is the only one that is frequently used in daily clinical practice when describing the history of neurological and non-neurological diseases.

Based on the different cardinal symptoms of Wilson's illness, a precise classification and differential diagnosis can be made33. Wilson's illness needs to be taken into consideration early in the differential diagnosis process, especially in cases of ambiguous extrapyramidal, hepatic, and psychiatric symptoms, in light of our understanding of its clinical subtypes

Type of progression (clinical variant)	Key clinical symptoms
Non-neurological mechanisms of progression 1. Hepatic (abdominal) 2. Preclinical (asymptomatic)	Acute and chronic liver disease that is decompensated, Hepatic cirrhosis None; a diagnosis was made before symptoms appeared
Advancement in neurological terms 1. Pseudoparkinsonism (tremulous and muscle stiffness) 2. Pseudosclerotic (tremulous) tremors 3. Hybrid form (arrhythmic-hyperkinetic)	Minor resting tremors, rigidity, hypomimia, dysarthria, hypersalivation, postural intentional tremors and bradykinesia Acroataxia, dysarthria, postural, flapping, and purposeful Parkinson's disease is accompanied by choreatic, athetotic, and torsio dyskinesia

Fig. 6: Clinical Symptoms 34

3. Based on the symptoms presentation, Wilson's illness is categorized as the following³⁷.

Wilson's disease (H) of the liver

H1: Acute Hepato Wilson's disease

H2: long-term Hepato Wilson's illness

Neurologic Wilson's diseases

N1: Hepatic involvement in conjunction with neurologic symptoms

N2: Just neurological symptoms

NX: Unclear connection with liver

COMPLICACY

Wilson's disease may be lethal if left untreated. Serious side effects include:

1. Liver cirrhosis: Scar tissue develops inside the liver as liver cells attempt to heal the injury resulting from too much copper, making it harder for the liver to operate³⁸.

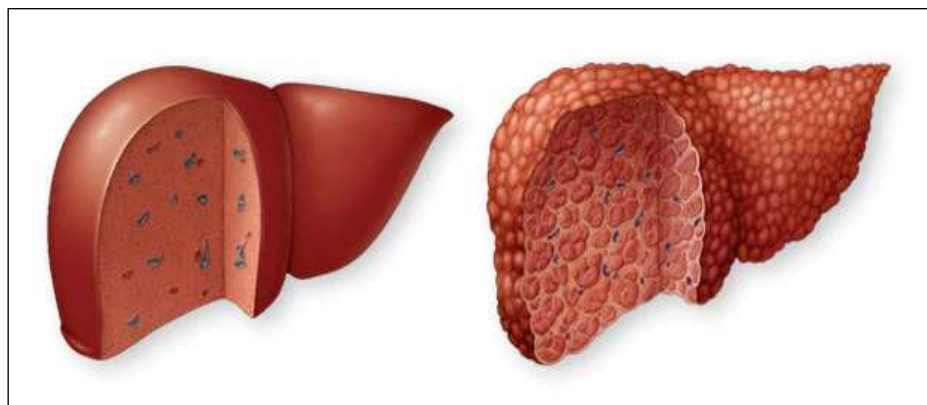


Figure 7: Normal liver v/s Cirrhosis liver³⁸

2. Liver disease: This can develop gradually over years or suddenly (hepatic failure that is acute). Treatment options could include a liver transplant.
3. Persistent neurological issues: Treatment for WD typically makes tremors, involuntary muscle movements, clumsy gait, and speech impairments better. However, some patients continue to experience neurological problems despite treatment³⁸.
4. Kidney problem: WD can harm the kidneys, which can result in issues like kidney stones and an unusual amount of amino acids being discharged in the urine.
5. Psychological problem: Changes in personality, depression, irritability, bipolar disorder, or psychosis are a few examples of these.
6. Blood issues. These could include haemolysis, which results in anaemia and jaundice by destroying red blood cells³⁸.

Wilson Disease during Pregnancy:

According to several publications on pregnant WD patients, pregnancies ended successfully for individuals with well-controlled WD when their condition was maintained to be treated and closely monitored³⁹. The condition usually appears in people in their early 20s. Due to the lowered fertility carried on by liver deficiencies, the likelihood of a successful pregnancy is significantly reduced in the absence of effective therapy. Intrauterine growth restriction and preeclampsia may be linked by disturbed copper metabolism. Patients with liver cirrhosis are less likely to have a successful pregnancy⁴⁰. Analysis of birth abnormalities, spontaneous abortion rate, and maternal problems during pregnancy was done in relation to prenatal care⁴⁰. Wilson's disease can be difficult to diagnose in pregnant women⁴².

Pregnancy is safe for WD patients receiving anticopper treatment. Compared to patients who had never received medication, the rate of spontaneous abortion was reduced in

treated patients⁴⁰. Similar to how copper-containing contraceptive devices work, abortion also works in this way, which is a contraceptive in nature and is active due to copper-deposited endometrial ions⁴⁴.

Medically treated WD patients with a confirmed diagnosis had considerably fewer spontaneous abortions than WD patients without a diagnosis (odds ratio, 2.853; 95% confidence range, 1.634-4.982). Of the 209 live births, 7 (3%) had birth abnormalities⁴⁰.

Even in individuals who have liver failure aggravation, the appropriate continuous treatment of Wilson's disease and replenishment of coagulation factors and/or platelets when required considerably boost the probability of a healthy pregnancy⁴⁵.

If no surgical operations were performed before birth, the patient can resume the dose they were taking prior to becoming pregnant. If a surgery was conducted at the birth, it is advisable to resume the decreased dose till The wound recovery is achieved^{4,50}.

Complications Faced during Pregnancy:

1. Hepatic dysfunction may be due to pregnancy-specific complications such as hyperemesis gravidarum, preeclampsia or acute fatty liver of pregnancy. The foetus was diagnosed with short limbs, microcephaly and early-onset growth restriction which were diagnosed before starting zinc therapy, the cause of which is unknown.
2. It is possible that initiation of zinc therapy at the initial admission (15 weeks) might have delayed or prevented the progression of disease process which manifested later with neurologic symptoms⁴².
3. The decrease in liver function tests was seen in 16 of 282 (6%) pregnancies, and it could be seen in both undiagnosed patients and those receiving therapy. After delivery, all liver test abnormalities disappeared. Although it was uncommon (1%), neurological problems that

worsened during pregnancy sometimes persisted after birth⁴⁰.

- Obstacles to the utilisation of a number of investigations for diagnosis present a problem to doctors since changes during pregnancy can replicate some clinical symptoms of chronic liver disease, such as spider naevi (Obstacles to the utilisation of a number of investigations for diagnosis present a problem to doctors since changes during pregnancy can replicate some clinical symptoms of chronic liver disease, such as spider naevi. The majority of pre-existing, newly developed, or pregnancy-specific hepatological diseases can be diagnosed with the aid of a high index of suspicion, team-based approach, utilisation of appropriate safe tests, including viral serology, antigen-specific antibodies copper-based studies, and ultrasound⁴³). The majority of pre-existing, newly developed, or pregnancy-specific hepatological diseases can be diagnosed with the aid of a high index of suspicion, team-based approach, utilisation of appropriate safe tests, including viral serology, antigen-specific antibodies copper-based studies, and ultrasound⁵¹.

Treatment Options with complexities:

- Chelating agent therapy (including D-penicillamine and trientine) and zinc salts have been connected with good consequences for both the mother and infant⁴⁶.
- Zinc: Administration of zinc during pregnancy at a dose of 25 to 50 mg three times per day seems to be effective with very little teratogenicity⁴¹. In contrast to chelating drugs, zinc can also be safely used during pregnancy despite a dose modification. If there are worries about persisting chelation during the pregnancy, changing from chelation therapy to zinc before becoming pregnant is a choice. The patient might not accommodate zinc well because of potential increased reflux and dyspepsia problems, which are frequent during pregnancy, therefore changing from chelation to zinc upon their gestation is not indicated⁴⁷.
- D- Penicillamine: - This medicine has been demonstrated in animal experiments to be teratogenic, at doses six times greater than those used therapeutically in humans. Skeletal abnormalities, cleft palates and prenatal toxicity (resorptions) have been observed. There are no coordinated studies on pregnancy in humans. Although normal results have been recorded, distinctive congenital cutis laxa (characterised with skin that is wrinkly and inelastic)⁴⁸ and related birth abnormalities have been

recorded in infants with women who received this medicine during pregnancy⁴⁹.

3.3% of kids born to DPA-using mothers, 2.7% of babies born to trientine-using mothers, and 0% of the babies born to zinc-using mothers experienced foetal abnormalities⁵¹.

Breast milk from mothers who had been treated for Wilson's Disease had a normal amount of copper in it. They did not appear to be noticeably higher or lower when compared to nursing mothers who were not taking treatment for the condition. Patients with Wilson's illness can safely breastfeed while taking their medications, according to the study⁵².

Since Wilson disease affects pregnant people as well as the foetus and offspring, pregnancy in such patients becomes a pertinent concern for medical practitioners⁴⁶.

TREATMENT:

WD requires lifelong treatment that aims to reduce copper levels to safety limits, stop the disease from progressing, and attempt to alleviate all symptoms and signs that have emerged as a consequence of body accumulating copper. Treatment may be divided up into three stages:

- The management of symptomatic patients
- Maintenance therapy following a copper reduction in damaged tissues and
- Maintenance therapy may be begun immediately in the case of asymptomatic patients.

This section is subdivided into three parts: Ayurvedic management, Allopathic management, and other treatment.

1. Allopathic Treatment:

Physiotherapy, appropriate follow-up, and changes in lifestyle are the therapeutic modalities. To safeguard against internal organ impairment, chelating agent dosage titration is advised if disease management is not established after the initial course of therapy⁵³.

Three different kinds of drugs are used to treat Wilson disease. First are drugs like penicillamine (Cuprimine) and trientine dihydrochloride (Syprine), which remove copper from the body by urination. Next are zinc salts, which stop the gut from absorbing copper from food, and third is tetrathiomolybdate, which both stops absorption of copper and binds toxic copper within the blood, rendering it nontoxic.

Table 1: Drugs with mechanism of action, treatment of duration and side effects⁵⁴

Drug	Symptoms	Method of action	Route of administration	Treatment duration	Side effects
d- Penicillinase	Symptomatic Wilson diseases	Chelates copper and promotes urinary excretion.	Oral	Typically it takes 1-2 years. In people with severe neuro disabilities, up to 3 years.	Lymphadenopathy, lupus like syndrome, worsening neurologic symptoms, Fever, rash, anaemia, bone marrow suppression.
Trientine	Symptomatic Wilson diseases	Chelates copper and promotes urinary excretion.	Oral	Typically it takes 1-2 years. In people with severe neuro disabilities, up to 3 years.	Proteinuria, autoimmune responses, deterioration, neurologic problems, and bone marrow suppression.

Zinc salts	Asymptomatic Wilson diseases	Induced metallothionein in gastrointestinal epithelial and inhibits absorption of copper.	Oral	Lifelong	Gastrointestinal upset
d- penicillinase, Trientine, Zinc salts	During pregnancy	copper chelator (penicillamine or trientine); Induced metallothionein in gastrointestinal epithelial and inhibits copper absorption (zinc)	oral	Optimise treatment before planned pregnancy Continue penicillamine or trientine; reduce dose by 25% or zinc	Avoid breastfeeding after delivery since oral copper chelators and zinc salts are released in breast milk and may affect the baby's ability to metabolise copper.
Dimercaprol or British anti-Lewisite or BAL	Severe, symptomatic primarily used in conjunction with oral copper chelating medications and is infrequently used for Wilson disease	chelate copper	parenteral	intramuscular injection for 2 to 10 days	nausea, vomiting, headache, dizziness, spasms, excessive sweating, lacrimation, or salivation, and tingling, burning, or discomfort on the skin or in the body. Seizures, stupor, and coma are uncommon but serious adverse effects ⁶³ .

2. Ayurvedic Treatment:



Ayurvedic treatments are supportive management used along with Allopathic management.




Let's understand it with a case study. A 12-year-old boy with Wilson's disease complained of trouble speaking, swallowing difficulties, and general stiffness for six months. His tests

revealed splenomegaly, a chronic parenchymal disease of the liver, SGPT 43 U/L, Ceruloplasmin 0.03 g/L, urine copper level 225.03 g per 24 hours, and other findings⁵⁵.

The general stiffness with hepatomegaly and splenomegaly in this case, according to Ayurveda, was related to Agnimandya at the Dhatu level, which resulted in Vatavyadhi, Yakrutodara, and Plihodara. ⁵⁶.

Table 2: Ayurvedic Treatment of Wilson Disease ⁵⁷⁻⁵⁹

Treatment	Components	Image
Vatavyadhi	Snehana (oleation),	 Fig 8. Snehana ⁵⁵
	MruduSwedana (mild sedation),	 Fig 9. Mrudu Swedana ⁵⁶

	Anuvasana Basti (oil enema)	
		Fig 10. Anuvasana Basti ⁵⁷
Yakrutodara and Plihodara	Niruha Basti (Decoction Enema)	
		Fig 11. Niruha Basti ⁵⁹
	Anuvasana Basti (oil enema)	
		Fig 12. Anuvasana Basti ⁵⁷

Oral medications, abhyanga, swedana, and basti were used to treat the illness. Following treatment, the symptoms were less severe and he could fully extend both lower limbs. His urine copper level returned to normal (47.01 g per 24 hours), leading to the conclusion that the Ayurveda method and dietary changes for such patients may help with supportive care and enhancing quality of life.⁵⁵.

There are some herbs used as a supportive treatment for Wilson's disease. They are

1. *Rhizoma Curcumae Longae*,
2. *Rhizoma Curcumae*,
3. *Radix Curcumae*
4. *Radix Curcumae*
5. *Rhizoma Coptidis*
6. *Herba Scutellariae Barbatae*
7. *Herba Andrographis*

1. *Curcumin*: an active ingredient from commonly used herbs like *Rhizoma Curcumae Longae*, *Rhizoma Curcumae*, *Radix Curcumae*, and *Radix Curcumae* can partially restore protein expression of most ATP7B mutants to restore functional copper export. Furthermore, curcumin is an ideal antioxidant, and an effective scavenger of reactive oxygen species and it exerts an anti-fibrotic effect by regulating hepatic stellate cell (HSCs) function ⁵⁸.

2. *Radix et Rhizoma Rhei*: The active ingredients in rhubarb root contain anti-oxidant, anti-fibrotic, and anti-inflammatory properties. ⁵⁸.

3. *Rhizoma Coptidis*: Anti-fibrotic and anti-oxidant activities were produced by berberine from *Rhizoma Coptidis*. ³¹.

4. *Herba Scutellariae Barbatae*: By controlling pre-mRNA splicing, P-coumaric acid from *Herba Scutellariae Barbatae* can restore the function of ATP7B and has anti-oxidative properties ⁵⁸.

5. *Herba Andrographis*: The active ingredient in herb andrographis, andrographolide, demonstrated anti-inflammatory activity by lowering the production of pro-inflammatory mediators and hepatoprotective benefits by inhibiting oxidative stress. ⁵⁸.

3. Other Treatment:

- Dietician recommends Cu Restriction diet: Foods like chocolate are completely forbidden since they contain excessive amounts of copper. Other foods with high copper content include nuts and oilseeds, condiments, and spices.
- Amla and Jambu fruit, Ridge gourd, Pumpkin, Mango green, French beans, Drumstick, Cluster Beans, Radish Pink, Sweet Potato, ArrowRoot, Cabbage, Dry Mango, and Drumstick leaves are only a few of the foods that contain copper in small amounts. To better prevent and manage Wilson's disease, one should adhere to this pathya (diet).
- For those who have severe liver failure, a liver transplant may be lifesaving ⁶⁰.

Wilson disease medication withdrawal can result in a quick buildup of copper and potentially fatal situations. Nutritional supplements may not be bioequivalent to zinc acetate and may not be as effective as the prescription version of this medication (Galzin).

IN-CLINICAL-TRIAL DRUGS FOR WILSON DISEASES:

Bis-choline tetra thiomolybdate - a phase II study demonstrating bis-choline tetra thiomolybdate in treating 28 people with Wilson's disease (WD).

- After 24 weeks of treatment, 71% of patients had attained the primary goal of normalised non-ceruloplasmin-bound copper (NCC) (57%) or a reduction of NCC of 25% or more (14%).
- An improvement in neurological status followed this. In 39% of patients who took at least 30 mg/day,

transaminases and gamma-glutamyl transferase levels increased in a reversible manner.

- 11 significant adverse events were reported in 25% of patients, 7 of which were not likely to be caused by the study medicine⁶¹.
1. **ALXN1840:** An oral dose ranging from 15 to 60 milligrams (mg) per day, can selectively bind to and remove copper from the body's tissues and blood.
 - A total of 214 subjects, including those who had never received treatment before and those who had, on average, received SoC treatment for ten years or more, were enrolled in the phase III trial, which evaluated the efficacy and safety of ALXN1840 versus standard-of-care (SoC) therapy in Wilson disease patients aged 12 or older.
 - Chelation therapy using penicillamine or trientine, zinc therapy, or chelation combined with zinc therapy were all included in the SoC.
 - Positive high-level trial data demonstrated ALXN1840's superiority to SoC by offering a statistically significant improvement in daily mean copper mobilisation from tissues. Additionally, compared to SoC, the medication increased copper mobilisation by almost three times. Therefore, Alexion's medication successfully treats Wilson illness in a Phase III trial⁶².

CONCLUSION:

Wilson disease is a rare inherited autosomal recessive genetic ailment that affects the brain, liver, eyes, and other crucial organs, among other places. Wilson disease is brought on by aberrant copper accumulation in the body. Another name for this is hepatolenticular degeneration. Other crucial organs can also be impacted, although the liver and basal ganglia of the brain are its primary targets. It shows different symptoms related to various affected sites and to diagnose the WD, different screening, as well as blood tests, are present. WD can be treated with copper chelating agents and Herbs act as a supporting treatment. Some drugs are still in the clinical trial phase.

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