WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Brief Review on Wilson Disease

Mr. Krushna V Zarekar [A], Ms. Pranali Hatwar[b], Dr. Gajanan S Sanap [A,B]*

LBYP College of Pharmacy, Chh. Sambhajinagar- 431111, Maharashtra, India
**Corresponding Author Email: krushnazarekar099@gmail.com*

A B S T R A C T

Wilson's disease is a rare Autosomal recessive defect, congenital disease or genetic abnormality. Caused by accumulating copper to in your liver, brain and other vital organs accumulation of copper leads to organ failure. daily copper intake plays important role in the development of good health and excess copper is essential to excreting its done by ATP7B. carrying ATPase family and encodes a protein with multiple transmembrane domains, an ATPase consensus sequence, a hinge domain, a phosphorylation site, and at least 2 putative copper-binding sites, over 200 mutations in the WD gene have been detected, leading to impaired ATP7B function and ultimately copper accumulation. However, excess copper can lead to free radical reactions and lipid peroxidation. The resulting liver damage can lead to fatty liver, inflammation, cirrhosis, and sometimes fulminant liver failure. Diagnosis of WD is usually based on typical clinical and laboratory findings, including low serum ceruloplasmin, increased urinary copper excretion, and increased hepatic copper levels. Because liver morphology is nonspecific and copper histochemistry can lead to false-negative and false-positive results, pathologists often only suspect disease or help confirm disease. Although the value of molecular genetic testing is limited by the large number of possible genetic mutations, the polymerase chain reaction may be useful in evaluating family members who are homozygous for dextrorotatory patients

Keywords: Wilson disease (WD), Liver transplantation**,** ATP7B, Liver disease, Penicillamine

1. Introduction

An inherited disorder that causes too much copper to accumulate in the organs In Wilson's disease ,copper isn't eliminated properly and instead accumulates ,possibly to a life-threatening level.[4] Symptoms typically begin between the ages of 12 and 23.Symptoms include swelling, fatigue, abdominal pain and uncontrolled or poorly coordinated movements.[8,9,11] Treatment often includes medication that can prompt the organs to release copper in to the blood stream Once it's in the bloodstream, it can then be eliminated from the body through the kidneys Initially described by Kinnear Wilson in 1912, Wilson's disease (WD, or Wilson disease),is the clinical condition resulting from mutations in the chromosome 13q14 in the region coding for the protein product ATP7B, and occurs in a sporadic fashion as well as inherited as an autosomal recessive disease Homozygous, or, more commonly ,compound heterozygous mutations lead to defective incorporation of copper into apo-ceruloplasmin and the subsequent formation of hollow ceruloplasmin, hampering the normal excretion of copperinto bile.[33,36] Impaired copper metabolism and subsequent copper intoxication are consequences of this condition.[11] With a shorter half-life than that of hole ceruloplasmin, circulating ceruloplasmin (ceruloplasmin) are abnormally low, albeit the gene responsible for thisprotein, localized on chromosome 3, is intact · providing one of the most important clinical diagnostic tools for WD [18,11,].Copper over load, and actually free copper as the main acting element, exerts its toxicity through two main mechanism's: Direct oxidative stress, withlipid peroxidation of membranes, DNA, and mitochondria, as well as due to un regulated apoptosis leading to cell death from copper-induced changes in the anti-apoptotic protein, X-linked inhibitor of apoptosis, and its loss of inhibitory control of caspase-3· It is now knownthat it is not the accumulation of copper itself what is deleterious to the organism, but rather free copper in the blood, which determines copper in toxication, as opposed to ceruloplasmin-bound copper.[36] Thus, the old paradigm of eliminating copper stores as the therapeutic objective has given way to the concept of normalizing free copper concentrations in the blood stream.[4,25,19] It should be stated that much of the knowledge that has accumulated in thedecades following the first description of the disease, as well as the mainstays of treatment,derive greatly from experts' opinions and some from anecdotal experiences, and not on adequately designed randomized comparativestudies.[4,18]

2.Signs And Symptom Sof Wilson's Disease

Wilson's disease is present at birth, but signs and symptoms only appear when copper builds up in the brain, liver, or other organs.[1,3,] Signs and symptoms vary depending on the part of the body that is affected by the disease.[1,]

they can include

- Fatigue, lack of appetite or abdominal pain
- A yellowing of the skin and the whites of the eye (jaundice).

- Golden-brown eye discoloration (Kayser-Fleischer rings).
- Fluid buildup in the legs or abdomen.
- Problems with speech, swallowing or physical coordination.
- Uncontrolled movements or muscle stiffness.
- CNC disorder, behavioral,dystonia,dysarthria,excessivesalivation,dysphagia. [1,2,3,38,39]

Fig. 1 Signs And Symptoms Of Wilson's Disease[39]

SCARRING OF THE LIVER (CIRRHOSIS)

As liver cells attempt to repair the damage caused by excess copper, the liver develops scar tissue which makes it harder for the liver to function.[36]

LIVER SYMPTOMS

People with Wilson disease often develop symptoms of hepatitis (inflammation of the liver) and can have an abrupt decrease in liver function (acute liver failure).[1,3,] These symptoms mayinclude

Some people with Wilson disease have symptoms only if they develop chronic liverdiseaseandcomplicationsfromcirrhosis.These symptoms may include

- Fatigue and weakness.
- Unexpected weightloss.
- Bloating from a buildup of fluid in the abdomen(ascites).
- Swelling of the lower legs, ankles or feet(edema).
- Itchy skin.
- Severe jaundice. [1,2,3,39]

CENTRAL NERVOUS SYSTEM SYMPTOMS

People with Wilson disease may affect central nervous system symptoms that affect their mental health as copper builds up in their body. These symptoms are more common in adults but do also occur in children.[4,9]

Neurological symptoms may include

- Problems speaking, swallowing, or coordination.[39]
- Muscle stiffness.[3]
- Shaking or uncontrolled movements.[2]

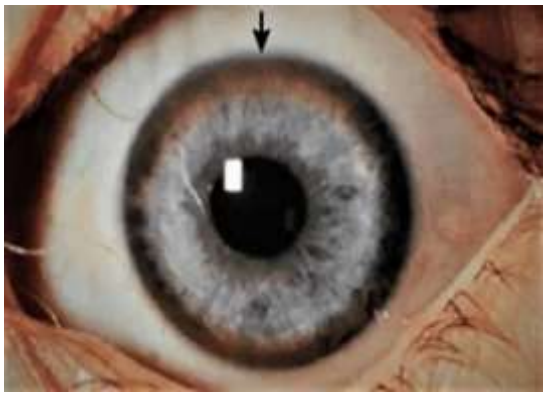
Symptoms of Wilson's disease that affect a person's mental health include

- Anxiety.[1,4,7]
- Changes in mood.[11,12]
- personality or behavior changes, Depression.[4,8]

- Confusion of thoughts and feelings that makes it difficult to tell what is real and what is not (psychopathy).[11]

Eye symptoms/Kayser-Fleischer rings

Kayser-Fleischer rings (K-F rings), also called Fleischer-Kayser rings or Fleischer-Strumpell rings, are the most common ophthalmic manifestation of Wilson disease.[4,8,9] KR Rings A golden brown or greenish yellow, bronze or reddish brown ring can be seen around the cornea. This happens due to the deposition of copper particles in the cornea



- Present in 98%with neurological involvement
- Present in 50% with hepatic involvement
- Can be difficult to sure even with slit lamp
- Sunflower cataracts
- A **golden brown ring**

Fig. Kayser-Fleischer rings

. Excess circulating copper deposits in Descemet's membrane extending less than 5 mm through cornea from Schwalbe's line[1,]

Appearance:

The KF ring is usually a raised golden brown ring around the cornea. It can also appear in chartreuse, ruby red, emerald green or ultramarine blue. It is almost always bilateral, first between 10-2 hours, then lower, then localized.[1] The KF ring is located at Descemet's membrane, beginning at the line of Schwalbe and extending less than 5 mm above the cornea.[1,3]

Examination:

This can be seen in an eyepiece slit lamp biomicroscope using **a** cobalt filter. In the early stages of the disease, gonioscopy is often necessary to detect t his subtle finding, but in advanced case**s** and in lightcolored irises, it can be seen with the naked eye.[1,2] Scheimpflug imaging to detect and quantify t he KayserFleischer ring, which appears as a bright peripheral subendothelial band**,** has also been described for the study of KR rings**.**[1,3] Recently, ant erior segment optical coherence tomography (ASOCT) has been shown to be effective in identifying the KayserFleischer ring as a strong hyperreflectiv e zone at Descemet**'s** peripheral corneal membrane, even with copper deposition. minimal[1,2].The gold standard for the detection and evaluation of Ka yserFleischer rings remains slit lamp examination.[5]However, its identification can be difficult mainly for inexperienced ophthalmologists in people with brown eyes or in the early stages of the disease, in which case gonioscopy is recommended.[1,2]

Kidney

Wilson's disease can damage the kidneys, leading to problems such as kidney stones and an abnormal number of amino acids excreted in the urine. Psychological problems. These might include personality changes, depression, irritability, bipolar disorder or psychosis. Blood problems.[3]

Other symptoms

Frequently early symtoms include difficulty speaking, excessive salivation, ataxia, maskikie farcies, clumsiness with the hand and personality changes late manifestation (know rare because of earlier diagnostic and treatment) include dystonia ,spasticity grand mal seizures ,rigidity, and flexion contactures. and the itching associated with Wilson syndrome can be quite annoying ,and even madding.[3,7,8]

3. Causes of Wilson Disease

An alteration (sometimes referred to as a mutation) in the ATP7B gene is the root cause of Wilson’s illness.

The gene provides instructions for making a protein called coppertransporting ATPase 2, which plays a role in transporting copper from the liver to the rest of the body.Copper is necessary for many cellular functions but can be toxic in excess.[39] The copper-carrying protein ATPase 2 is particularly important for removing excess copper from the body.[39] Variations in the ATP7B gene prevent the transporter from working properly.[4,8,9] Excess copper cannot be excreted from the body due to lack of functional proteins. As a result, copper builds up to toxic levels that can damage tissues and organs, especially the liver and brain. Studies have shown that normal variations in the PRNP gene can alter the course of Wilson's disease. The PRNP gene provides instructions for making the prion protein, which is active in the brain and other tissues and appears to be involved in copper transport. The study focused on the effect of a variant of the PRNP gene that affects position 129 of the prion protein. In this position, humans can have the protein building block (amino acid) methionine or the amino acid valine. Methionine rather than valine at position 129 of the prion protein appears to be associated

with delayed onset of symptoms and increased incidence of neurological symptoms, particularly tremors, in people with the ATP7B gene variant. However, larger studies are needed before the impact of this PRNP gene variant on Wilson disease can be determined.[39]

Copper Metabolism-

Copper is an essential trace element and an important cofactor for many enzymes required for cellular respiration, iron oxidation, pigment formation, neurotransmitter biosynthesis, antioxidant defense, and bond formation[1] . Copper The recommended intake of is approximately 0.9 mg/Day, and the average diet meets this need, consuming approximately 2-5 mg intakePer day[1]. Since the major route of copper excretion is biliary excretion of, the liver plays an important role in-copper metabolism by regulating biliary copper excretion.[8] The C Pathways of copper homeostasis are summarized in and [21,12] of Copper is absorbed in the proximal small intestine and transported by the copper transport enzyme

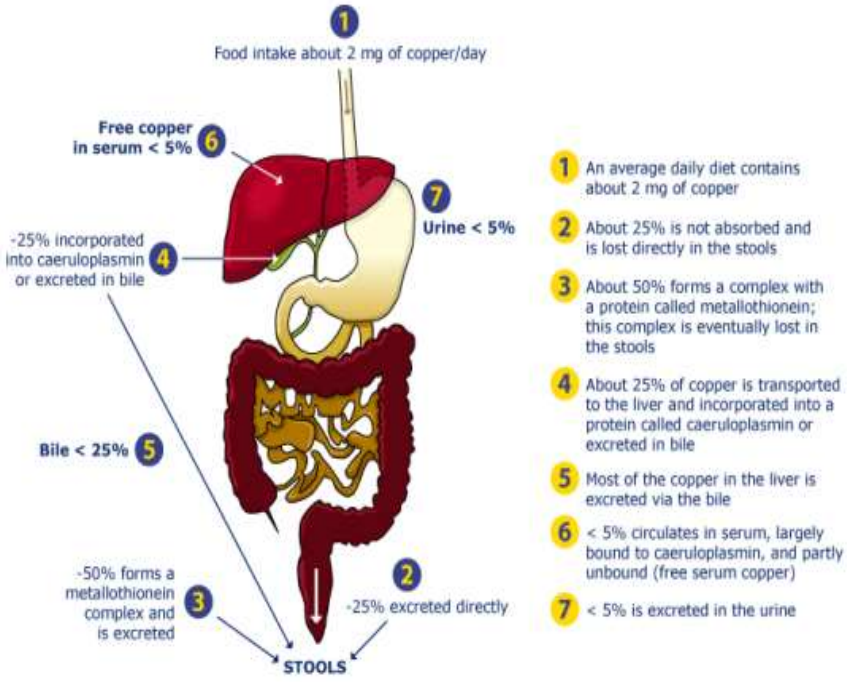


Fig. Healthy routine copper metabolism[35]

ATP7A through enterocytes to the portal circulation, where it is loosely bound to albumin[7]. Copper-Is transported into hepatocytes via the copper transporter-Protein (CTR-1), which is located on the sinusoidal side of hepatocytes.liver cells[6]. Copper binds to the metallic chaperone in the cell because he does not exist in ionic or free form. Metallochaperone is a small protein that delivers copper per to specific cellular targets [24] . One such copper chaperone, ATOX1, supplies copper to the Wilson's disease protein, ATP7B, through copper-dependent protein-protein interactions [9]. CCS1 (copper chaperone for superoxidedismutase) supplies copper to superoxide dismutase (SOD1)[23]. This is primarily a cytoplasmic defines against Oxidative stress [18]. ATP7B is present in the transGolgi network in Cases of normal and low copper conditions and is critical for Holoceruloplasmin synthesis [21]. In the presence of excess copper, ATP7B migrates to the canalicular side, where it facilitates biliary copper excretion [16] . ATP7B-dependent biliary copper excretion is a major homeostatic mechanism of copper metabolism [3]. Biliary excretion of copper also occurs through conjugation with glutathione [8] .But it is lowAffinity pathway compared with ATP7B-dependentBiliary copper excretion [15]. Therefore, the liver uses some copper for its metabolic needs, including the synthesis and secretion of ceruloplasmin (copper-containing protein), which is also involved in iron metabolism [14]. ExcessCopper is excreted in the bile in normal individuals, but is not excreted in patients with Wilson's disease[11]

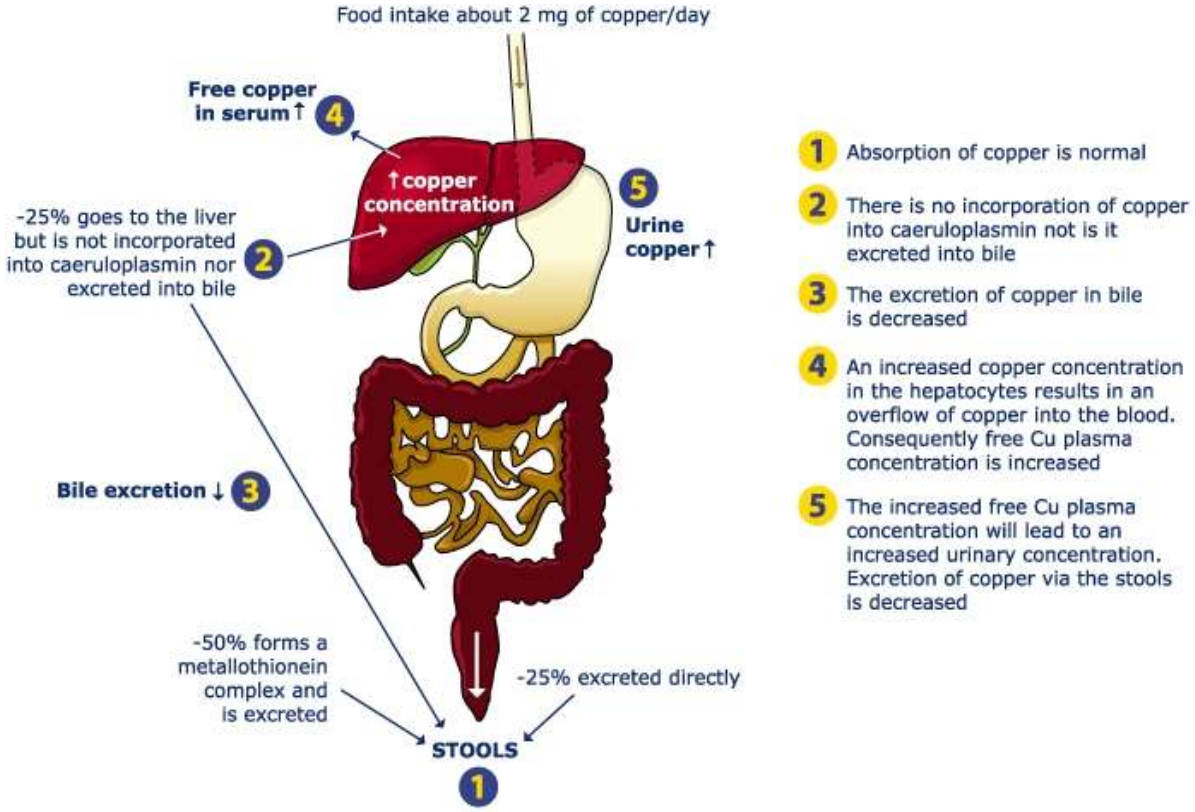


Fig. Reduced excretion and retention of copper[35]

Molecular Pathogenesis

Wilson's disease results from mutations in the ATP7B geneThat are inherited in an autosomal recessive manner [19,12]. The ATP7B Gene, located on the Long arm of chromosome 13, encodes a Copper-transporting P-type ATPase located at Intracellular [22]. The protein ATP7B is involved in copper uptake intoceruloplasmin and Copper excretion in bile [17]. ATP7B mutations result in a missing or non-functional ATPase With defects in synthesis of cerulo-Plasmin and defects in biliary copper excretion [13]. The Resulting accumulation of copper in the liver and extrahepatic tissues causes copper toxicity With myriad clinical features of Wilson's disease [18]. As a pro-oxidant, copper produces Sufficient Reactive oxygen that damages cells[2]. Copper-Also induces apoptosis by Conformational changes Of the anti-apoptotic protein, X-linked inhibitor of apoptosis (XIAP)[3].summarizes the etiology of copper toxicity[7]. More than 500 ATP7B mutations Have been reported in Wilson disease[2]. Despite extensive efforts to prove correlations, no Clear genotype- The phenotypic pattern remains elusive[2]. It is found in-patients of Eastern European descent and is more common in the elderly with Neurological manifestations[16]Genetic factors may attenuate or enhance them and may affect mutated genes[4]

Liver Disease-

The nature of liver disease ranges from biochemical abnormalities to all types of liver disease, including acute hepatitis, acute liver failure, and cirrhosis with portal hypertension [9] . Symptoms of liver disease are common in children [1]. Children may be asymptomatic and may present with hepatomegaly or abnormal Serum aminotransferases [7] .Some patients present with no immune-mediated (negative hemolytic Combs' anemia), which may be accompanied by transient episodes of Jaundice or mild hemolysis[12]. Acute liver failure is the most dramatic presentation, andCan occur in catastrophic idiopathic episodes [7] .It is thought to be rare, accounting for only 3% (n=9) of ALF cases in the U.S[9]. pediatric ALF series,and is associated with high mortality, 95% in some registries[23] . has been reached. Wilson disease 30% of allCases[7]. In the Kings College Hospital series , our own Series , and the Egyptian series 88 literature, the disease has been observed more frequently in boys Than in girls[24] . Most of the patients in our series were hisBefore puberty[18]. Both negative Coombs hemolytic anemia and renal insufficiency maycontribute to the clinical picture[5]. Again, this points to significant geographic differences.Negative Comb hemolysis is commonly present and may be a characteristic diagnostic feature, especially in patients with jaundice or acute liver failure[7].In a large Japanese series, hemolytic anemia was the only feature present inPatients, (1.0%) patients with progressive acute liver failure[8] .Encephalopathy with cerebral edema develops in [19].Previously treated patients who discontinue medication may also exhibit acute rapid deterioration, which is of particular concern when patients present.At first onset in puberty or adolescence[15].Splenomegaly can be an important clinical clue for the diagnosis of patients with hypersplenism or those with evidence of chronic liver disease. Showshis Patients with Wilson's disease with liver disease across five series[17]. Summary of clinical features[16] .

4. Diagnosis Of Wilson Disease

The diagnosis of Wilson's disease can be difficult because its signs and symptoms are often hard to distinguish from other liver diseases, such as.In addition, symptoms may change with time.Making a link between incremental behavioural changes and those of Wilson can be particularly challenging.[3,4,40]

Physical exam-

During a physical exam, physician will check for signs of liver damage for example

- Changes in skin the skin
- Enlargement of the liver or spleen.
- Tenderness or swelling in the abdomen.
- Swelling in the lower legs ,feet, or ankles called edema.
- Yellowish color of the whites of the eyes [1,3,36,39,36,40]

Eye exam-

During a slit-lamp exam a physician will use a special light tolook for kayser-fleisher ring in patient eye [1,37]

Tests and procedures used to diagnose Wilson's disease include

- Blood and urine tests.
- Eye exam .
- Removing a sample of liver tissue for testing (biopsy
- Genetic testing .
- Leipzig score .
- LFT (liver function test) .
- KFT (kidney function test)
- MRI (Magnetic resonance imaging. [1,3,5,]

Physician typically use blood tests and a 24-hour urine collection test to diagnose Wilson disease. Doctors may also use a liver biopsy and BODY imaging tests.[1]

Blood test-

For a blood test, a health care professional will take a blood sample send the sample to a lab.and physician may order one or more blood tests, including tests that check amounts of

- ceruloplasmin, a protein that carries copper in the bloodstream. People with Wilson disease often have low ceruloplasmin levels, but not always[1]
- copper. People with Wilson disease may have lower than normal blood copper levels. Acute liver failure due to Wilson disease may cause high blood copper levels[1]
- liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST).[1] People with Wilson disease may have abnormal ALT and AST level
- red blood cells to look for signs of anemia.[1]

Doctors may order a blood test to check for the gene mutations that cause Wilson disease if other medical tests don't confirm or rule out a diagnosis of the disease.[1,2]

24-Hour Urine Collection Test/Copper Urine Test-

For 24 hours, you will collect your urine at home in a special container that is copper-free, provided by a health care professional. A health care professional will send the urine to a lab, which will check the amount of copper in your urine. Copper levels in the urine are often higher than normal in people who have Wilson disease[1]

Liver biopsy-

If the test of blood and urine tests can't confirm or rule out a diagnosis of Wilson's disease, your physician may order a liver biopsy. During a liver biopsy, a physician will take a small part of the tissue from your liver. [1,38]

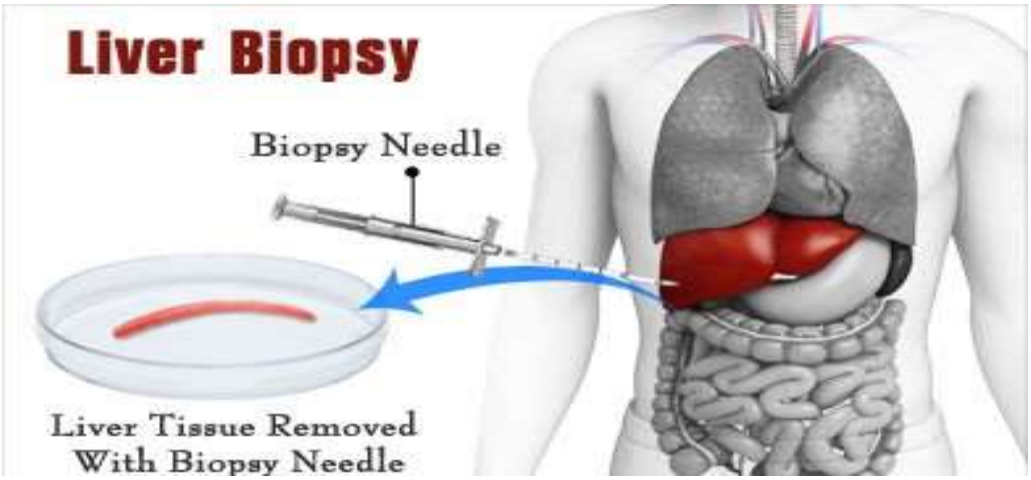


Fig. liver biopsy

A pathologist will examine the tissue under a microscope to look for features of specific liver diseases, such as Wilson disease, and check for liver damage and cirrhosis. A part from liver tissue will be sent to a lab, which will check the amount of copper in the tissue.[1,38]

Imaging tests-

In patient who have nervous system symptoms, physician may use imaging tests to check for signs of Wilson disease or other conditions in the brain.[1.38]

Physician may use

- magnetic resonance imaging (MRI) NIH external link, which uses radio waves and magnets to produce detailed images of organs and soft tissues without using x-rays[38]
- computed tomography (CT) scan NIH external link, which uses a combination of x-rays and computer technology to create images[1,38]

5. Treatment:

Wilson disease treat with

- medicines that remove copper from the body, called chelating agents[4]
- zinc, which prevents/avoid the intestines from absorbing copper[4]

In many cases, treatment can avoid or prevent symptoms and organ damage. Doctors may also recommend changing your diet to avoid foods that are reach in copper. People who have Wilson's disease need life-long treatment.[4] Discontinue treatment may cause acute liver failure. Doctors daily perform blood and urine tests to check how the treatment is working.[12,13,17]

Treatment for Wilson disease focuses on achieving a loss of copper balance either with chelators (drugs that promote cupriuresis) or zinc which decreases absorption or both[5]. Liver transplantation is indicated in patients with acute liver failure, unresponsive to medical treatment or those with end-stage liver disease[3]. Drugs available for the treatment of Wilson's disease include D-Penicillamine, Trientine, 4 Ammonium tetra the molybdenum and Zinc [6]. It should be remembered that these drugs have not been subjected to randomized controlled trials,71 and trials are underway to clarify these issues[1].

D-penicillamine :

Dimercaprol was used as a chelating agent until the introduction of D-penicillamine in 1956. Since then, it has been extensively studied and advocated in the treatment of Wilson’s disease [2]. Penicillamine is a degradation product of penicillin with a free sulfhydryl Group that acts as a Copper chelator [7]. D-Penicillamine may also act by inducing Metallothionein, thereby promoting copper urine and sequestering free copper. The major excretion route is via the kidney [9].D-penicillamine started at a dose of 250-500 mg/day,He increased by 250 mg every 4-7 days, divided into 2-4 doses he1000-1500 mg/day Increase. The Maintenance dose is usually 750 to 1000 mg daily, which he gives in two divided doses. An analysis of one and 12 observational studies found that D-penicillamineIs probably the most effective drug in liver disease Wilson’s disease.) usually occurs 2 to 6 months after treatment [2]. Failure to comply can lead to progression of liver failure over the next 1-12 months [6]. Among chelating agents, D-penicillamine had the highest neurological deterioration [11]

Trientine:

Trientine was introduced in 1982 as an alternative to D-peni-Sylamine given its side effect profile [6].It is a Chelator with a polyamine-like structure and no sulfhydryl Groups[8]. It forms a stable complex with four of her Constituent nitrogen atoms in a planar ring [4]. Trientine also chelates iron and co-administration of trientine and iron-Should be avoided because the complex with iron is toxic. Data on the pharmacokinetics of Tri-Are lacking [1] . Trientine is particularly preferred in patients with D-penicillamine intolerance or neurological symptoms as it causes less neurological exacerbation than D-penicillamine [8].Mentioned in like [4]. There are encouraging data on the use of trientine in patients with severe liver disease [5]. Used for maintenance therapy [1].

Zinc acetate (Galzin):

This medicine avoid your body from absorbing copper from the meal you eat. It is typically used as maintenance therapy to avoid copper from store again after treatment with penicillamine or trientine. Zinc acetate might be used as primary therapy if you don't take penicillamine or trientine. Zinc acetate can cause stomach upset.[4,8,11,13]

Liver Transplantation for Wilson Disease:

Wilson's disease (WD) requires lifelong treatment, and most patients can be treated successfully with drug therapy and a low-copper diet.[1] Although WM is a very treatable disease, approximately 5-10% of patients with WM require liver transplantation.[4] This includes patients who are diagnosed with the disease after developing severe liver damage that does not respond to the drug alone, including some patients who previously had treatable disease but stopped taking the drug and developed WD in due to acute liver failure.[36] Unexplained liver failure, although very rare, can occur in patients despite taking their medications faithfully, often due to concurrent liver disease.[9] When the liver can no longer function properly, the damaged organ can be surgically removed and replaced with a healthy liver or part of a donor liver. In a liver transplant, the new organ can come from a deceased donor or from a living donor. Liver transplantation is a life-saving treatment option for WD patients with chronic or sudden liver failure.[36] A record 9,000 liver transplants will be performed in the United States in 2021.[4] Between 1987 and 2008, 570 adults and children with WD underwent liver transplantation.[36]

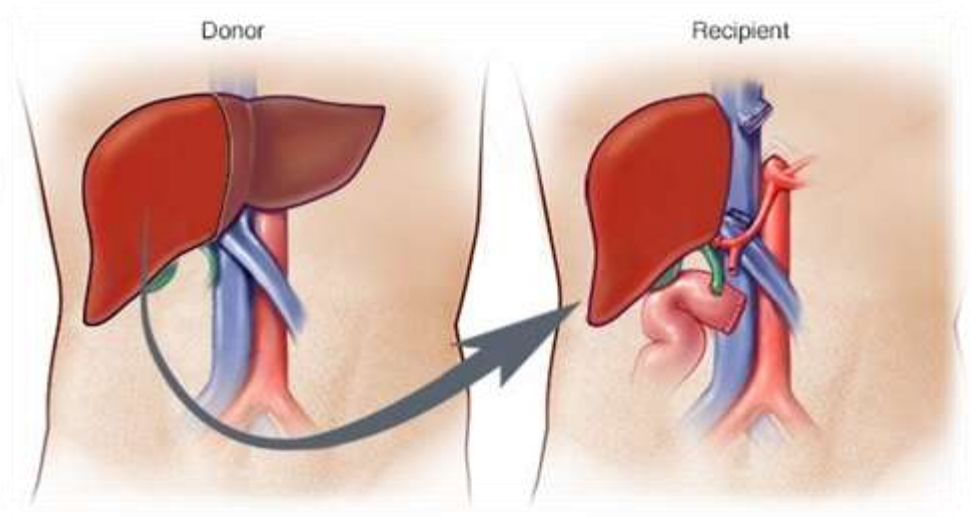


FIG. liver transplant [34]

With transplantation, the disease is actually Elimination because the inherited metabolic defect that causes WM resides in damaged liver hepatocytes.[18] However, patients who receive organ transplants must take a variety of medications to avoid rejection of the new organ for the rest of their lives.[36]

When Liver Transplant is needed

Treatment for Wilson Disease

Wilson's disease (WD) is a highly treatable condition as long as the patient is detected early with normal liver function and the patient is faithfully taking the appropriate medications for life.[36] The treatment works by reducing or eliminating dietary copper build-up or preventing copper build-up in the body. Copper chelators, including penicillamine and trientine, may be prescribed.[10] Zinc therapy, which blocks copper absorption, is another treatment option, but it is primarily approved for maintenance therapy or treatment of asymptomatic patients.[36] A low copper diet is also recommended by limiting or avoiding foods such as chocolate, nuts, shellfish, organ meats and mushrooms and paying attention to copper levels in water.[4] Why treatment may not work In other cases, people with WD may not respond to any treatment options.[9] Some patients may have advanced liver failure at the time of diagnosis, which cannot be treated with medication. In rare cases, unexplained liver failure may occur in WD Patients who take their medications faithfully, usually due to other causes of liver damage unrelated to WD.[11] Although WD treatment is very effective in halting disease progression and sometimes reversing symptoms, some patients are unable to adhere to their medications and diet.[36] Non-adherence means using medications or not taking them regularly and as directed.[4] Studies on various diseases have shown that non-adherence to treatment regimens can range from 20 to 50

percent. WD patients who never develop symptoms of the disease due to early diagnosis or who experience side effects from medications may be at higher risk.[36] It is extremely important that people with WD follow their doctor's treatment recommendations and monitor their treatment regularly throughout their lives! In these cases, liver transplantation may be the only remaining treatment option. Signs that may require a transplant WD patients with stable liver disease should still have routine and laboratory tests twice a year, and more frequently in those with abnormal tests.[4] The whites of the eyes will also appear yellow.[9] Fluid retention and edema (swelling) in the lower extremities may occur in some patients, and abdominal distension due to ascites may occur.[36] Other symptoms that indicate liver failure include Loss of appetite and weight loss Right upper quadrant tenderness Itching Nausea, vomiting, diarrhoea, light stools, dark urine Poor blood clotting Drowsiness Confusion, irritability and mood changes When to Seek Care a doctor If you or a family member notices any of the physical or emotional changes above, it's important to see your doctor right away! Liver failure progresses rapidly, so symptoms should not be ignored.[36]

If when laboratory and other diagnostic tests determine that the liver is severely damaged and unlikely to regenerate or heal on its own, the patient should be evaluated for liver transplantation at a transplant centre and liver transplantation may be recommended.[9] When to be evaluated for a transplant your doctor will tell you if it is time to be evaluated for a liver transplant.[4] The first step is to identify, if possible, the nearest medical centre to you that has a liver transplant program.[4] Due to the limited number of organs available for transplantation, the number of centres with qualified and licensed medical teams to perform liver transplantation is also limited.[9] Consideration should also be given to selecting a centre with the capacity to perform a living donor liver transplant, as this will increase the chances of obtaining an organ in a timely manner if a potential donor is available.[36] Family members who are carriers of WM may also be suitable donors and should not be excluded on the basis of carrier alone.[4] Graft evaluation takes several days and may require hospitalization.[9] If a child is being assessed, a parent or guardian must be present during the hospital stay.[4] The evaluation involves several medical tests, including blood tests, heart tests, possible liver biopsy, ultrasound or CT scans and MRIs, lung and kidney function tests.[36] Assessments are performed by several specialists in the transplant team.[4] The transplant team includes herpetologists, transplant surgeons, transplant coordinators, nurses, social workers, psychologists, and other specialists who may need specialized care.[4] Transplantation is a major operation and the maintenance of the recipient's organ requires long-term care and follow-up, so the transplant team must ensure that the patient receives appropriate family and emotional support.[36]

6. CONCLUSIONS:

Wilson disease is an inherited metabolic disease which results in copper accumulation affecting mainly the liver and neurological systems. It should be suspected especially in children and young adults presenting with jaundice, acute liver failure or chronic liver disease. Diagnosis of Wilson disease can be made using the scoring system incorporating routinely available laboratory tests. ATP 7 B gene mutation when identified in a proband is helpful in identifying pre-symptomatic siblings and is the highest weighted variable in the Leipzig score. Haplotype analysis or direct sequencing is useful for screening of siblings. However, if one can establish a diagnosis on clinical grounds alone, there may not be a need for genetic testing. Wilson disease carries an excellent prognosis if diagnosed and treated early and if compliance with treatment is maintained. The outcome may be less desirable in those with neurologic disabilities. Drugs have excellent efficacy but has to be monitored at regular intervals. Liver transplantation may be indicated in those who present with acute liver failure or those unresponsive to medical management. Siblings need to be screened and started on treatment preferably with Zinc to prevent disease manifestation

7. ACKNOWLEDGEMENT

I would like to express my genuine thanks Dr. Gajanan Sanap, Principal, LBYP college of Pharmacy, for giving me this opportunity to carry out my study in the LBYP (Afflicted University DBATU) Maharashtra, India.

References

1. **https://medicomaestro.com/kayser-fleischer-ring/**
2. **https://wilsondisease.org/medical-professionals/signs-and-symptoms/**
3. **https://www.niddk.nih.gov/health-information/liver-disease/wilson-disease/diagnosis#:~:text=What%20tests%20do%20doctors%20use,liver%20biopsy%20and%20imaging%20tests.**
4. Patil, Mallikarjun, et al. "A review and current perspective on Wilson disease." Journal of clinical
5. Bull P.C., Thomas G.R., Rommens J.M. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet. 1993;5:327–337. [PubMed] [Google Scholar]
6. Tanzi R.E., Petrukhin K., Chernov I. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet. 1993;5:344–350. [PubMed] [Google Scholar]
7. Tanzi R.E., Petrukhin K., Chernov I. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet. 1993;5:344–350. [PubMed] [Google Scholar]

8. Yamaguchi Y., Heiny M.E., Gitlin J.D. Isolation and characterization of a human liver cDNA as a candidate gene for Wilson disease. BiochemBiophys Res Commun. 1993;197:271–277. [PubMed] [Google Scholar]

9. Das, Shyamal K., and Kunal Ray. "Wilson's disease: an update." Nature clinical practice Neurology 2.9 (2006): 482-493.

10. Thomas G.R., Roberts E.A., Walshe J.M. Haplotypes and mutations in Wilson disease. Am J Hum Genet. 1995;56:1315–1319. [PMC free article] [PubMed] [Google Scholar]

11. Kim G.H., Yang J.Y., Park J.Y. Estimation of Wilson's disease incidence and carrier frequency in the Korean population by screening ATP7B major mutations in newborn filter papers using the SYBR green intercalator method based on the amplification refractory mutation system. Genet Test. 2008;12:395–399. [PubMed] [Google Scholar]

12. Payne, Aimee S., Edward J. Kelly, and Jonathan D. Gitlin. "Functional expression of the Wilson disease protein reveals mislocalization and impaired copper-dependent trafficking of the common H1069Q mutation." Proceedings of the National Academy of Sciences 95.18 (1998): 10854-10859. Abdel Ghaffar T.Y., Elsayed S.M., Elnaghy S. Phenotypic and genetic characterization of a cohort of pediatric Wilson BRIEF REVIEW ON WILSON DISEASE Page 17 disease patients. BMC Pediatr. 2011;11:56. [PMC free article] [PubMed] [Google Scholar]

13. Devarbhavi H., Singh R., Adarsh C.K. The clinical, laboratory characteristics, natural history and outcome in 201 patients with Wilson disease. Hepatology. 2012;56(suppl S1):826A. [Abstract] [Google Scholar]

14. Taly A.B., Prashanth L.K., Sinha S. Wilson's disease: an Indian perspective. Neurol India. 2009;57:528–540. [PubMed] [Google Scholar]

15. Rodriguez-Castro, Kryssia Isabel, Francisco Javier Hevia-Urrutia, and Giacomo Carlo Sturniolo. "Wilson's disease: A review of what we have learned." World journal of hepatology 7.29 (2015): 2859.

16. Wilson S. Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver. Brain. 1912:295–509. [PubMed] [Google Scholar]

17. Schilsky, Michael L. "Wilson disease: current status and the future." Biochimie 91.10 (2009): 1278-1281.]

18. Rosencrantz R, Schilsky M. Wilson disease: pathogenesis and clinical considerations in diagnosis and treatment. Semin Liver Dis. 2011;31:245– 259. [PubMed] [Google Scholar]

19. Hoogenraad TU. Paradigm shift in treatment of Wilson's disease: zinc therapy now treatment of choice. Brain Dev. 2006;28:141–146. [PubMed] [Google Scholar]

20. .Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. Lancet. 2007;369:397–408. [PubMed] [Google Scholar]

21. Scheinberg IH, Sternlieb I. Wilson's disease. In: Smith JL, editor. Major problems in internal medicine. Philadelphia: WB Saunders; 1984. pp. 25– 35. [Google Scholar]

22. Scheinberg I, Sternlieb I. Wilson Disease. In: Lloyd H, Smith J, editors. Major Problems in Internal Medicine. Saunders: Philadelphia; 1984. p. 23. [Google Scholar]

23. Available from: http://www.wilsondisease.med.ualberta.ca/database. BRIEF REVIEW ON WILSON DISEASE Page 18

24. Caca K, Ferenci P, Kühn HJ, Polli C, Willgerodt H, Kunath B, Hermann W, Mössner J, Berr F. High prevalence of the H1069Q mutation in East German patients with Wilson disease: rapid detection of mutations by limited sequencing and phenotype-genotype analysis. J Hepatol. 2001;35:575– 581. [PubMed] [Google Scholar]

25. Kim EK, Yoo OJ, Song KY, Yoo HW, Choi SY, Cho SW, Hahn SH. Identification of three novel mutations and a high frequency of the Arg778Leu mutation in Korean patients with Wilson disease. Hum Mutat. 1998;11:275– 278. [PubMed] [Google Scholar]

26. Nanji MS, Nguyen VT, Kawasoe JH, Inui K, Endo F, Nakajima T, Anezaki T, Cox DW. Haplotype and mutation analysis in Japanese patients with Wilson disease. Am J Hum Genet. 1997;60:1423–1429. [PMC free article] [PubMed] [Google Scholar]

27. Wu ZY, Wang N, Lin MT, Fang L, Murong SX, Yu L. Mutation analysis and the correlation between genotype and phenotype of Arg778Leu mutation in chinese patients with Wilson disease. Arch Neurol. 2001;58:971– 976. [PubMed] [Google Scholar]

28. Thomas GR, Jensson O, Gudmundsson G, Thorsteinsson L, Cox DW. Wilson disease in Iceland: a clinical and genetic study. Am J Hum Genet. 1995;56:1140–1146. [PMC free article] [PubMed] [Google Scholar]

29. Margarit E, Bach V, Gómez D, Bruguera M, Jara P, Queralt R, Ballesta F. Mutation analysis of Wilson disease in the Spanish population -- identification of a prevalent substitution and eight novel mutations in the ATP7B gene. Clin Genet. 2005;68:61–68. [PubMed] [Google Scholar]

30. Beinhardt S, Leiss W, Stättermayer AF, Graziadei I, Zoller H, Stauber R, Maieron A, Datz C, Steindl-Munda P, Hofer H, et al. Long-term outcomes of patients with Wilson disease in a large Austrian cohort. ClinGastroenterolHepatol. 2014;12:683–689. [PubMed] [Google Scholar]

31. https://www.researchgate.net/figure/Defective-copper-metabolism-andpathogenesis-of-Wilsons-disease-Source-Semela-D_fig4_354023335 BRIEF REVIEW ON WILSON DISEASE Page 19

32. Shah, Hemangi B., et al. "Insights from analysis of human antigenspecific memory B cell repertoires." Frontiers in Immunology 9 (2019): 3064.

33. .Khan, S., et al. "Mutation profile in Wilson's disease from north Indian patients." International Journal of Human Genetics 12.2 (2012): 125-132.

34. https://medlineplus.gov/genetics/condition/wilson-disease/

35. https://my.clevelandclinic.org/health/diseases/5957-wilson-disease 31. Ferenci, Peter. "Diagnosis of Wilson disease." Handbook of clinical neurology 142 (2017): 171-180

36. http://www.eurowilson.org/en/living/guide/pathway/index.phtml

37. https://wilsondisease.org/living-with-wilson-disease/treatment/transplantation/#:~:text=Liver%20transplantation%20cures%20Wilson%20disease,and%20other%20long%2Dterm%20complications.

38. https://www.scientificanimations.com/wilsons-disease-symptoms-causes-and-treatment/blog/

39. Walshe, John M. "Cause of death in Wilson disease." Movement disorders: official journal of the Movement Disorder Society 22.15 (2007): 2216-2220.

40. https://www.mayoclinic.org/diseases-conditions/wilsons-disease/symptoms-causes/syc-20353251