Approaches in Hepatology

Hepatology Made Easy

Wilson's disease

❖ All you need to know About Wilson's disease:

- ✓ Wilson disease (WD) is an autosomal recessive disorder of copper metabolism caused by disease-specific defects in the ATP7B gene that encodes (ATPase) expressed primarily in the trans-Golgi network of hepatocytes.

- ✓ Loss of ATP7B function is responsible for defective biliary excretion of copper by liver cells that leads to pathologic accumulation of hepatic copper and secondary organ injury as well as defective copper incorporation into ceruloplasmin, which is a phenotypic marker in most patients with Wilson's disease.

- ✓ WD is an autosomal recessive disease with an incidence of 1/20,000 to 30,000 in most populations.

- ✓ Biliary excretion of copper is reduced in WD due to defective or absent ATP7B function, which may cause defective entry of cytosolic copper into the vesicular component of the excretory pathway to bile.

- ✓ Reduced biliary copper excretion in WD leads to pathologic hepatocellular copper accumulation.

- ✓ Hepatic copper accumulation and hepatocellular injury lead to increased circulating non-ceruloplasmin-bound copper, which is responsible for extrahepatic copper accumulation.

- ✓ Copper toxicity plays a primary role in the pathogenesis of extrahepatic manifestations of WD.
  - Affected organs, in particular the central nervous system, invariably exhibit elevated copper levels.
  - Pathologic copper deposition in the brain, mostly in the caudate nucleus and the putamen of the basal ganglia, results in the neurologic and psychiatric manifestations of the disease.
  - Excessive deposition of copper in the Descemet membrane of the cornea gives rise to [Kayser Fleischer (KF) rings] and rarely sunflower cataracts.

❖ Characteristic clinical features:

- ✓ Liver disease due to WD ranges from asymptomatic to chronic hepatitis, cirrhosis, and even acute liver failure (ALF). Most patients with symptomatic WD present clinically in the second or third decades of life with hepatic disease and in the third or fourth decades with neuropsychiatric features; however, patients have been diagnosed even into the eighth decade of life. Patients may be asymptomatic, although most present with hepatic or neurologic manifestations. Less commonly, patients are present with renal, skeletal, cardiac, ophthalmologic, endocrinologic, or dermatologic symptoms.

- ✓ Age of the patient: Clinical symptoms are rarely observed before age 3 to 5 years, and most untreated patients become symptomatic by the age of 40 years. Fewer patients present with WD after 50 years of age; the oldest reported siblings presented at 70 and 72 years of age.

- ✓ Frequency of symptoms
  - ➢ Hepatic in 42%,
  - ➢ Neurologic in 34%,
  - ➢ Psychiatric in 10%,
  - ➢ Hematologic in 12%.

- ✓ Hepatic symptoms usually are present in the second or third decade of life, and neurologic in the third and fourth decades.

Hepatic Manifestations

- It tends to occur at a younger age (mean, 10 to 12 years) than neurologic manifestations.
- The rate of progression of liver disease is variable in WD patients. Patients with asymptomatic disease typically have abnormalities of liver biochemical tests that correlate histologically with hepatic steatosis and inflammation.
- Ongoing inflammation leads to a progression of fibrosis and eventual cirrhosis with progressive hepatic insufficiency and liver failure. Complications of portal hypertension become evident with advancing cirrhosis.

Acute Liver Failure

- Patients tend to be young, in their second decade of life, and the clinical picture may be indistinguishable from that of viral-induced massive hepatic necrosis.
- Although serum aminotransferase levels are only mildly to moderately elevated, there is marked elevation of the serum bilirubin, a low serum alkaline phosphatase level, and evidence of Coombs-negative hemolytic anemia.

Neurologic features

- Neurologic involvement tends to occur in the third to fourth decades of life.
- The diagnosis of WD is often delayed for 1 to 2 years in patients in whom neurologic features predominate.
- Common early neurologic symptoms are dysarthria, clumsiness, tremor, drooling, gait disturbance, masklike facies, and deterioration of handwriting.
- Rigidity with overt Parkinsonian features, flexion contractures, and spasticity are seen less often and in the later stages of the disease.
- Athetosis (involuntary writhing movements) or a more severe movement disorder may be present. Rarely, generalized seizures may occur.
- Autonomic dysfunction may be present, most commonly in association with other advanced neurologic findings.
- Cognitive ability usually remains normal but may be impaired in patients with severe neurologic impairment.

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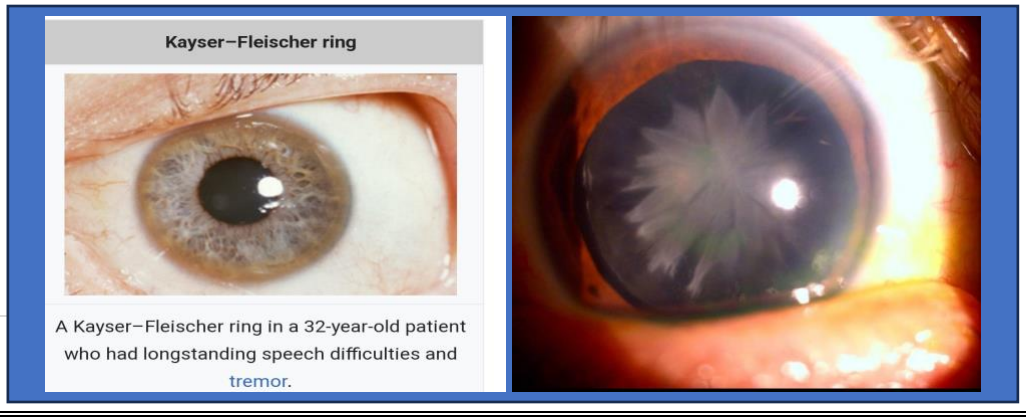
- Neurologic symptoms may improve markedly with medical treatment or after LT, although residual deficits are common, especially in those with long-standing symptoms before the onset of therapy.
- Magnetic resonance imaging (MRI) shows focal lesions in the putamen and globus pallidus and in some cases additional lesions in the pons and brainstem.

Psychiatric features

- Early symptoms in teenagers may be limited to subtle behavioral changes.
- Patients may present later with personality changes, lability of mood, emotionalism, impulsive and antisocial behavior, depression, and increased sexual preoccupation. Frank psychosis may occur.
- Psychiatric symptoms may resolve with medical therapy or after LT (transplant).

Ophthalmologic features

1. Kayser-Fleischer Rings: Electron-dense granules rich in copper and sulfur are deposited in the Descemet membrane of the cornea, creating the KF ring.



- The KF ring is golden brown or has a greenish discoloration in the limbus that is evident initially at the superior and inferior corneal poles on slit lamp examination of the cornea.
- The ring eventually becomes circumferential, and the width of the ring increases in untreated patients. KF rings diminish in size and may disappear with treatment, typically over months to years.

- The presence or absence of KF rings should be confirmed by an experienced ophthalmologist using a slit-lamp examination.

جهاز ال slit lamp مش retinoscope.

- KF rings are present in most symptomatic patients with WD and nearly always in those with neurologic manifestations; they are often absent in asymptomatic cases and in 40% to 50% of patients with hepatic disease.

- The reappearance after regression or new appearance of KF rings suggests nonadherence to medical therapy.

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- KF rings are not pathognomonic of WD because they also are seen occasionally in patients with long-standing cholestasis from other causes.

بردو هى ممكن تظهر فى ال long standing cholestasis خلى بالك 👌

2. Sunflower Cataracts: Typically observed in association with KF rings, but less frequently overall. Vision is not affected. It resolves with treatment of WD.

Renal features

- Findings include proximal renal tubular acidosis or features of Fanconi syndrome in patients with a chronic disease presentation.
- Acute tubular injury may occur in ALF due to WD from the large release of copper and copper complexes from injured liver cells.
- Distal renal tubular acidosis also may occur and may be responsible for the increased incidence of renal calculi in WD.
- Hematuria, mostly microscopic, may be caused by nephrolithiasis or glomerular disease.
- Proteinuria has been noted as a manifestation of WD, although nephrotic syndrome and Goodpasture syndrome are more likely to be a side effect of therapy with D-penicillamine or less commonly trientine.
- Chelation therapy usually results in marked improvement in renal function.

Skeletal features

- More than one half of patients with WD exhibit osteopenia caused by osteomalacia, osteoporosis, or both.

- Symptomatic arthropathy occurs in 25% to 50% of patients; this degenerative joint disease resembles osteoarthritis and involves the spine and large joints.
- Osteochondritis dissecans, chondromalacia patellae, and chondrocalcinosis have also been described.

- **Hemolysis:** An episode of acute intravascular hemolysis may be the presenting feature in up to 15% of patients; it is often transient and self-limited but can be associated with ALF due to WD

- **NAIL Abnormalities:** Azure lunulae (bluish discoloration of the lunules [bases] of fingernails) are an uncommon but characteristic finding.

- **Endocrine features:** Delayed puberty, gynecomastia, and amenorrhea have been noted. They occur most often in patients with advanced liver disease and may be due to hormonal imbalance from the liver disease and not to WD itself.

❖ Diagnosis:

✓ Considerations in the workup of Wilson disease are as follows:

1) Serum ceruloplasmin levels are less than 20 mg/dL (reference range, 20-40 mg/dL) in approximately 90% of all patients with Wilson disease.
2) Urinary copper over 24 hours: The urinary copper excretion rate is greater than 100 mcg/day (reference range, < 40 mcg/day) in most patients with symptomatic Wilson disease, but it may also be elevated in other cholestatic liver diseases.
3) Copper concentration in liver biopsy: Hepatic copper concentration (criterion standard) on a liver biopsy specimen is >250 mcg/g of dry weight even in asymptomatic patients; a normal result (15-55 mcg/g) effectively excludes the diagnosis of untreated Wilson disease, but elevation may be found in other chronic hepatic disorders.

✓ Notes:

- Serum ceruloplasmin levels are poorly predictive of WD in the acute setting; however, 24-hour urinary copper and circulating copper levels are markedly elevated.
- In a patient with Kayser-Fleischer rings, a serum ceruloplasmin level < 20 mg/dL and 24-hour urine copper excretion >40 mcg/day establish the diagnosis of Wilson disease.

- Liver biopsy, if performed (generally via a trans jugular route due to coagulopathy), demonstrates an elevated hepatic copper content and usually advanced fibrosis or cirrhosis with severe hepatocellular injury.

✓ WD should be considered in persons with:
- Unexplained serum aminotransferase elevations, chronic hepatitis with steatosis, poorly responsive autoimmune hepatitis, cirrhosis, and ALF
- Neurologic features of unexplained origin (abnormal behavior, incoordination, tremor, dyskinesia).
- A neurologic or psychiatric disorder with signs of concurrent hepatic disease.
- KF rings detected on routine eye examination.
- Unexplained, acquired Coombs-negative hemolytic anemia.
- A sibling or parent with a diagnosis of WD.

✓ Leipzig Criteria are shown below:

TABLE 19.1 ■ **Leipzig Criteria for the Diagnosis of Wilson Disease**

Typical Clinical Symptoms and Signs		Other Tests	
Kayser-Fleischer rings:		Liver copper (in the absence of cholestasis):	
Present	2	>5× ULN (>4 μmol/g)	2
Absent	0	0.8–4 μmol/g	1
		Normal (<0.8 μmol/g)	−1
		Rhodanine-positive granules[a]	1
Neurologic symptoms[b]:		Urinary copper (in the absence of acute hepatitis):	
Severe	2	Normal	0
Mild	1	1–2× ULN	1
Absent	0	>2× ULN	2
		Normal, but >5× ULN after D-penicillamine	2
Serum ceruloplasmin:		Mutation analysis:	
Normal (>0.2 g/L)	0	Mutations detected on both chromosomes	4
0.1–0.2 g/L	1	Mutations detected on 1 chromosome	1
<0.1 g/L	2	No mutations detected	0
Nonimmune-mediated hemolytic anemia:			
Present	1		
Absent	0		

Total Score	Interpretation
≥4	Diagnosis established
3	Diagnosis possible, more tests needed
≤2	Diagnosis unlikely

❖ Treatment

i. Diet: A low-copper diet is recommended. Foods with a high copper content (e.g., liver, chocolate, nuts, mushrooms, legumes, and shellfish) should be avoided.

ii. Drugs

ℛ D-Penicillamine (Artamine)

- Its mechanisms of action include copper chelation.
- Dose: 1–1.5 g/d (in divided doses BID or QID) {Artamine 250 mg tab}.
- It is best absorbed if taken on an empty stomach.
- Side effects include hypersensitivity, bone marrow suppression, proteinuria, systemic lupus erythematosus, and Goodpasture syndrome. Dermatologic side effects include pemphigus, acanthosis nigricans, and elastosis perforans serpiginosa.
  - You can avoid SE as possible as you can by gradual reintroduction of the drug. Bone marrow suppression or significant or worsening proteinuria (>1 g/24 hours) usually requires withdrawal of the drug.
  - If these side effects occur, D-penicillamine should be discontinued and appropriate alternative therapy instituted.
  - Small doses of pyridoxine (25 mg/day) should be given daily, because of the weak anti-pyridoxine effect of D-penicillamine.

- Note: Penicillamine should never be given as an initial treatment to patients with neurologic symptoms. The drug may also cause significant worsening of neurologic features or precipitate autoimmune features such as myasthenia, polymyositis, or systemic lupus erythematosus.

ℛ Trientine

- Trientine 1–1.5 g/d (in divided doses BID or QIB) dose is the same as D-penicillamine.
- New data suggest that this medication may possibly be given as a single daily dosage, thereby improving adherence and reducing inconvenience related to avoiding taking the medication with meals.
- This has similar side effects as penicillamine but at a lower frequency. Sideroblastic anemia is the only major side effect of this agent and occurs with overtreatment. Other infrequently reported side effects include skin rash, gastrointestinal distress and colitis, and, rarely, rhabdomyolysis. Most of the side effects of D-penicillamine, with the exception of elastosis perforans serpiginosa, subside when the patient is converted to Trientine
- The risk of neurologic worsening with trientine is less than with penicillamine.
- Due to its improved safety profile compared with D-penicillamine, this drug has been recommended as first-line therapy for patients with WD who start with chelation therapy; however, it is expensive.

ℛ Zinc

- Zinc salts administered orally in divided doses can be used for treatment of WD.
- Zinc is relatively safe; side effects include gastrointestinal upset and elevated amylase and lipase without clinical or imaging evidence of pancreatitis.
- Dose: 150 mg daily of zinc acetate in adults, divided into three doses between meals.
- The role of zinc in therapy is mainly in pre-symptomatic WD and as maintenance therapy in patients.
- Zinc monotherapy is not recommended as initial therapy for symptomatic patients, but good outcomes have been shown in patients with predominately neurologic disease, even when zinc is used as initial therapy.
- Outcomes are less satisfactory when zinc is used as a single agent to maintain patients with primary hepatic disease.

❖ **Treatment Protocol**

1. Initial therapy
   - A baseline 24-hour urinary copper determination, serum copper, ceruloplasmin, blood counts with platelets, international normalized ratio (INR), liver biochemical tests, and urinalysis should be obtained.
   - D-penicillamine or Trientine should be initiated in divided doses at 25% to 50% of the initial target dosage of 20 mg/kg over 2 to 4 weeks with monitoring.
   - Patients intolerant of D-penicillamine may be treated with Trientine or zinc.
   - Evidence of improvement in liver synthetic function or neurologic and psychiatric symptoms often begins within 6 to 12 months of uninterrupted therapy.
   - Patients with severe hepatic insufficiency unresponsive to pharmacotherapy, typically defined as 3 months of treatment, with a modified Nazer score of 10 or greater, should be considered for “liver transplantation” Nazer score is a score for severity and prognosis of Wilson’s disease.
2. Maintenance therapy
   - Once clinical symptoms and signs have stabilized, urinary excretion of copper is declining from baseline values, and the non-ceruloplasmin copper is reduced to <15 µg/dL, the dose of chelating agents should be reduced to maintenance ranges.
   - Maintenance dose of penicillamine is 10 to 15 mg/kg daily in divided dosages.
   - Neurologic disease: Approximately 20% of patients presenting with neurologic disease have worsening of neurologic symptoms during initial treatment with D-penicillamine or Trientine; this is most likely caused by the mobilization and redistribution of copper in the brain during initial treatment.

- A slow ramping up of the medication may reduce the frequency of this complication. Dose reduction or discontinuation of chelation treatment may be necessary if neurologic worsening occurs.

- Patients may be placed on zinc during this time. Alternatively, combination therapy with zinc and a lower dose of the chelating agent temporally spaced may prove to be an alternative treatment for these patients but has not been tested in clinical trial.

3. Liver transplantation
   - LT is curative for WD because the defect of the disease resides within hepatocytes. A complete reversal of the metabolic defect in copper metabolism is seen, as is improvement in hepatic and neurologic manifestations in most patients.

   - The majority of adults transplanted for WD have chronic liver failure. ALF is a more common indication in the pediatric population.

   - Patients with ALF due to WD have a relatively low alkaline phosphatase value that declines as the liver failure progresses--->Because these patients have hemolysis and elevations in the bilirubin occur rapidly.

   - The ratio of alkaline phosphatase to serum bilirubin is typically <4, and the AST to ALT ratio is >2.

   - If patients have these two biochemical parameters and a low hemoglobin level due to hemolysis, the sensitivity and specificity for the diagnosis of WD as the etiology for the ALF is nearly 100%.

   - Patients with ALF due to WD should be referred immediately for LT. Measures to stabilize the patient are directed at lowering the marked elevated levels of copper in the circulation.

   - This has been accomplished by several means, including exchange transfusion, plasmapheresis coupled with hemofiltration,

   - In the absence of severe hepatic disease, Liver Transplant for refractory neurologic manifestations should still be considered experimental; however, several reports have noted improvement in these patients after LT.

   - Patients with severe neurologic involvement do not always improve after LT, and poorer post-transplantation outcomes have been reported with respect to survival and complications from use of calcineurin inhibitors to prevent graft rejection.

❖ **Prognosis:**

Patients rarely survive longer than days to weeks unless liver transplantation is performed. Only rare patients may be rescued with medical therapy alone.