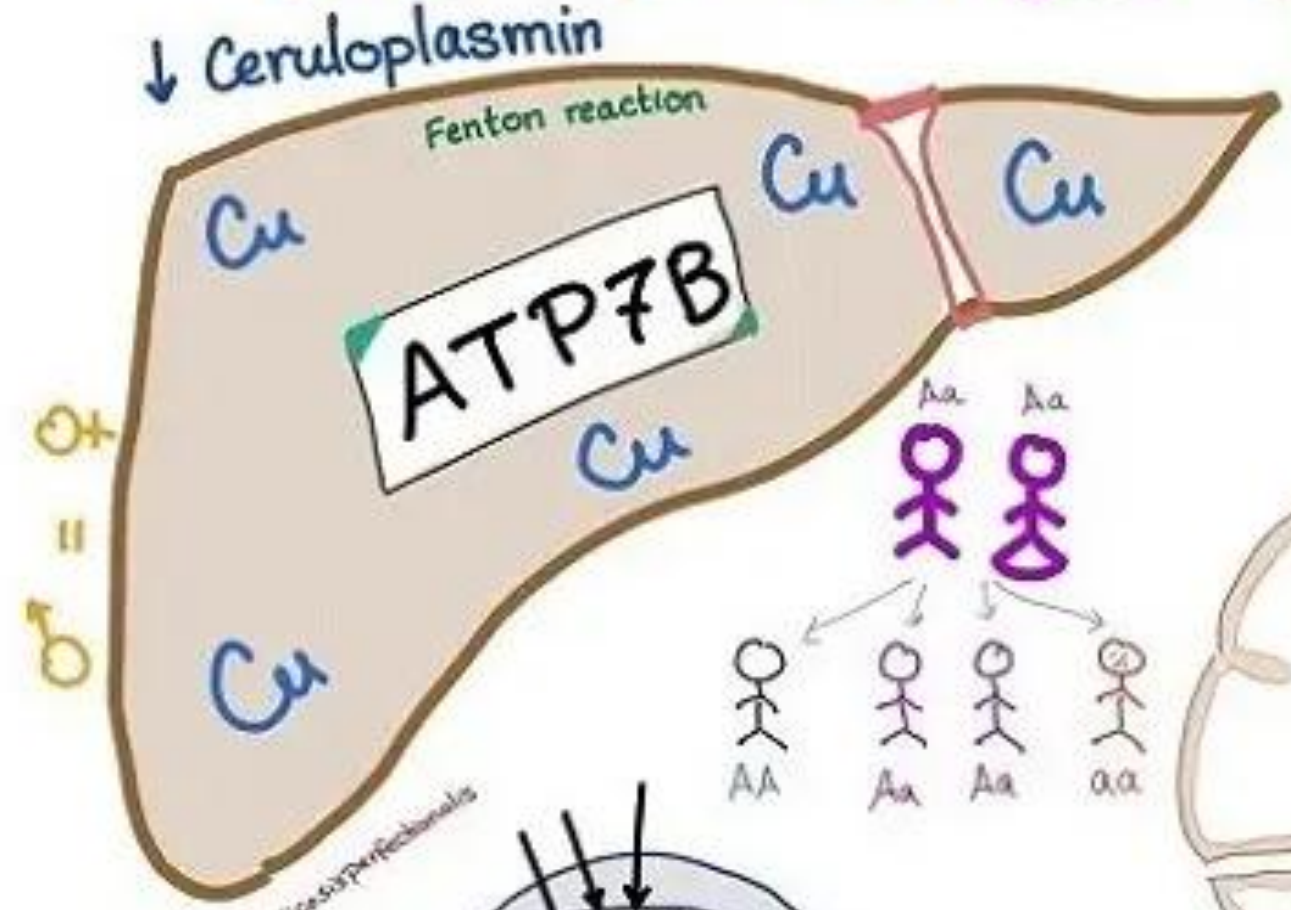
TEHRAN UNIVERSITY OF MEDICAL SCIENCES

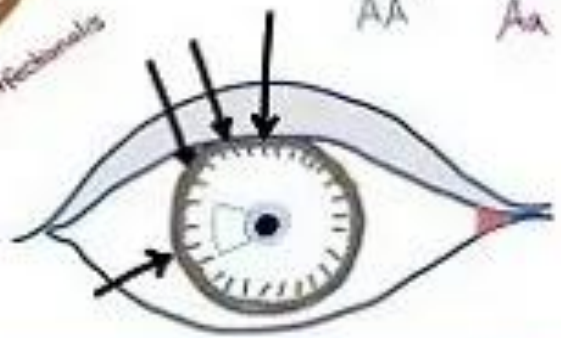
Wilson's Disease

DR. Z.M. SANAT

WILSON's Cu

"Hepatolenticular Degeneration"





Genetics

Wilson disease is an autosomal recessive disorder and is the result of pathogenic variants in *ATP7B*, a gene encoding a copper transport protein, ATP7B, on chromosome 13.

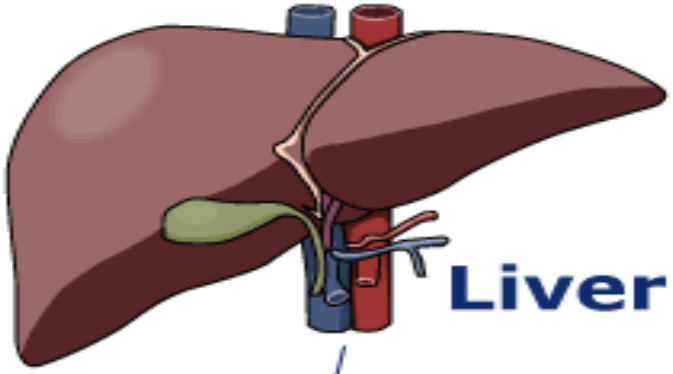
Biallelic, pathogenic (disease-causing) variants affecting both ***ATP7B*** **alleles** are required to develop Wilson disease.

Typically, one pathogenic variant is inherited from each parent.

Liver brain cornea

Wilson's Disease

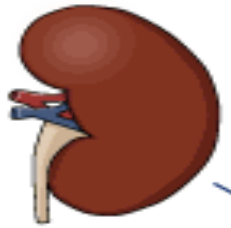
Liver



Hepatomegaly
Jaundice
Acute hepatitis
Fulminant hepatic failure
Portal hypertension: bleeding varices
Cirrhosis

Renal

Proximal renal tubular dysfunction



Bone

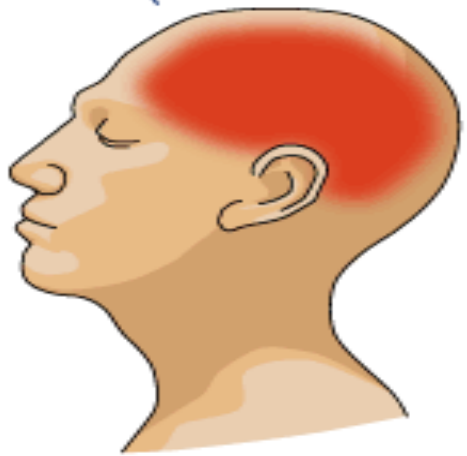
Arthritis
Rickets

Cardiac

Haem

Hemolysis

Central nervous system



Deterioration in school performance
Behavioral changes
Inco-ordination (handwriting deteriorates)
Resting and intention tremors
Dystonia
Dysarthria
Excessive salivation
Mask-like facies
Dysphagia

Eye

Kayser Fleischer rings

CLINICAL MANIFESTATIONS

- Hepatic
- Neurologic
- Psychiatric
- Non-immune hemolysis

Signs and symptoms

- Abdominal pain
- Jaundice
- Hepatomegaly
- Splenomegaly
- Ascites
- Upper gastrointestinal bleeding
- Stigmata of chronic liver disease
- Mental status changes due to hepatic encephalopathy

Age at symptom onset

For patients with Wilson disease,

a critical *ATP7B*-dependent copper excretory pathway fails to develop or is dysfunctional,

and copper accumulation that begins at birth continues throughout life,

gradually producing clinical disease .

The majority of patients with Wilson disease are diagnosed between the ages of 5 and 35 years

children, adolescents ,adult

children are more likely to present with hepatic manifestations and rarely with neurologic symptoms.

Adolescents and adult patients present more often with neurologic manifestations.

The mean age at presentation for patients with neurologic symptoms ranges between 15 and 21 years .

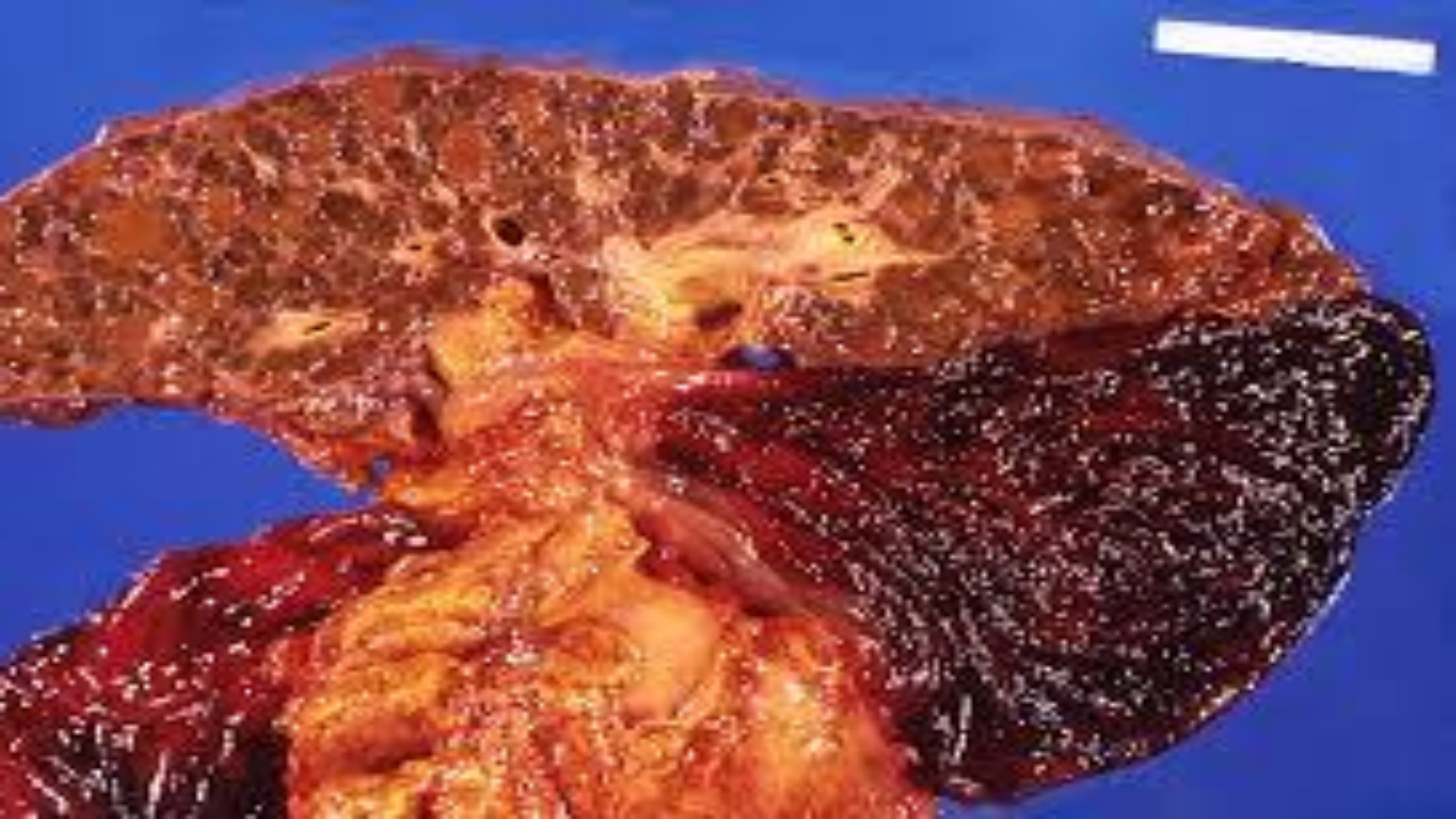
Age of onset

The variability in the age of onset of Wilson disease probably reflects differences in mutations and penetrance, extragenic factors, and environmental influences including diet

Hepatic disease

The liver is the initial site of copper accumulation in patients with Wilson disease, and there are several different clinical manifestations due to hepatic copper accumulation.

- asymptomatic biochemical abnormalities
- steatosis
- acute hepatitis
- acute liver failure (with an associated Coombs-negative hemolytic anemia)
- chronic hepatitis
- cirrhosis



Acute hepatitis and acute liver failure

Wilson disease accounts for approximately 5 percent of patients with acute liver failure who are referred for emergency transplantation.

The female to male ratio of patients with acute liver failure due to Wilson disease is 2:1 to 4:1

Chronic hepatitis and cirrhosis

Patients with chronic hepatitis due to Wilson disease are often asymptomatic from their liver disease.

after being found to have abnormal liver tests, or after presenting with neurologic or psychiatric manifestations of Wilson disease.

Wilson disease often results in hepatic steatosis and may be diagnosed in a patient being evaluated for nonalcoholic fatty liver disease

Serum aminotransferases

Serum aminotransferases are usually mildly to moderately elevated in patients with Wilson disease diagnosed in a pre symptomatic stage.

The aspartate aminotransferase (AST) concentration is usually higher than the alanine aminotransferase concentration (ALT)

Cirrhosis is present at the time of diagnosis of Wilson disease in approximately 35 to 45 percent of patients overall

Neurologic manifestations

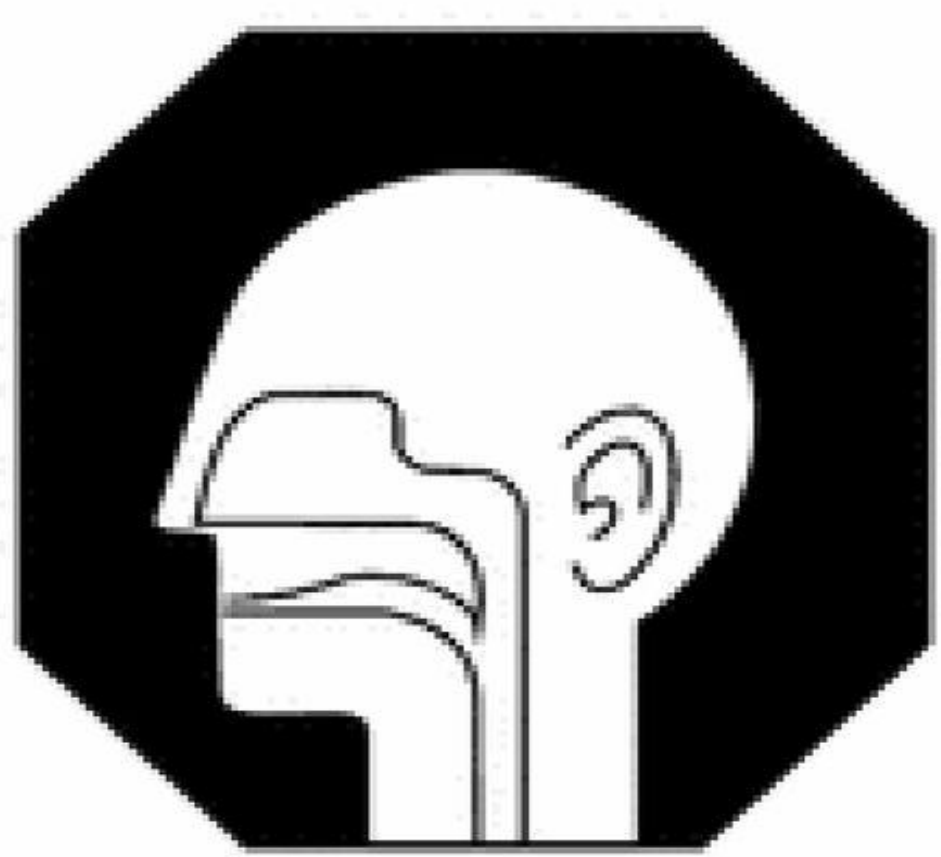
Nearly all (98 percent) of patients with Wilson disease with neurologic manifestations have Kayser-Fleischer rings.

Neurologic symptoms may be very subtle or may be rapidly progressive, leading to severe disability over the course of months.

- Dysarthria – 85 to 97 percent of patients with neurologic Wilson disease
- Gait abnormalities/ataxia – 30 to 75 percent
- Dystonia – 11 to 69 percent
- Tremor – 22 to 55 percent
- Parkinsonism – 19 to 62 percent
- Drooling

Dysarthria

- Dysarthria is a motor speech disorder.
- Dysarthria affects the movement of the individual speech muscles.
- It can vary from mild slurring to completely unintelligible speech



What is Dysarthria?

It is a condition when the muscles that a person uses for speaking weaken or it becomes difficult to control those muscles.

Drolling


disorder
job
business
neurological
diagnostic
medical
dystonia
form
diagnosis
work
health
stressful
office
worried
clinician
movement
complicated
biotechnology
surgical
depressed
syndrome
illness
symptoms
disease
thermometer
cardiogram
administration
chemical
dysautonomia
emotional
depression
pathology
heart
chaos
frustrated
stethoscope
challenge
vegetable
doctor
busy

chorea

Chorea

This is a genetic disorder which affects the functioning of the brain

Chorea is a medical condition and a type of movement disorder

Dystonia

Oromandibular Dystonia or Meige Syndrome
Involuntary opening, closing, or deviation of the jaw

Blepharospasm
Involuntary contractions of the muscles around the eyes

Advantages
- ✓ Adjustable
- ✓ Reversible
- ✓ Rechargeable

Spasmodic Dysphonia or laryngeal Dystonia
Affects the vocal cords to have strangled, hoarse quality or a breathy, whispering voce

Writers cramp, Musician's Dystonia
Involuntary movements, cramping and spasming of the hands or arms

Cervical Dystonia or Spasmodic Torticollis
Affects the neck muscles leading to abnormal movements of the head and neck

Limb Dystonia
Involuntary movements, cramping and spasming of the legs or feet

Deep Brain Stimulation Surgery is an effective treatment method for Dystonia

Ocular manifestations

Kayser-Fleischer rings are brownish rings that are due to fine, pigmented, granular deposits of copper in Descemet's membrane in the cornea .

Kayser-Fleischer rings are a characteristic feature of Wilson disease and are seen in approximately 98 percent of patients with neurologic manifestations, but only 50 percent of patients with hepatic manifestations.


Kayser-Fleischer ring

While often only detected by slit-lamp examination (typically done in a patient already suspected of having Wilson disease),

Kayser-Fleischer rings are sometimes visible without a slit-lamp examination when they are sizable

Psychiatric manifestations

- Depression
- Declining school performance
- Personality changes (which may be subtle)
- Irritability
- Impulsiveness
- Labile mood


MOOD
Disorders

Wilson disease should be considered in

1-Patients with liver abnormalities of uncertain etiology

2-Pediatric patients, and less commonly adults,

with clinical features suggestive of autoimmune hepatitis, especially if there is no response or inadequate response to standard treatments for autoimmune hepatitis with glucocorticoids, as there have been rare instances of concurrent disease.

3-Patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis (steatosis is a common finding in Wilson disease)

with atypical features for nonalcoholic fatty liver disease

4-Patients with acute liver failure with features suggestive of Wilson disease.

5-First-degree relatives of a patient diagnosed with Wilson disease.

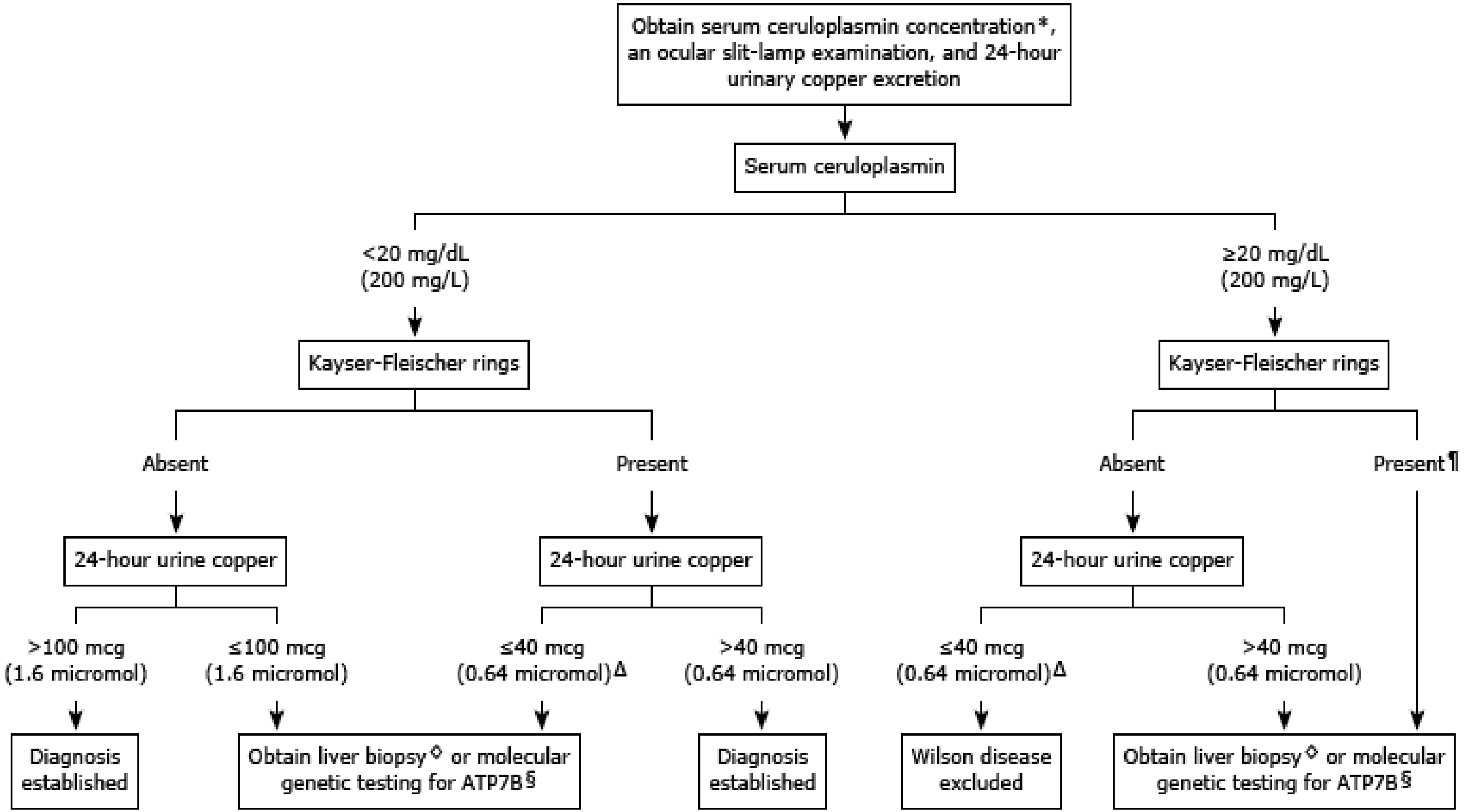
6-neurologic abnormalities

7 -psychiatric abnormalities

DIAGNOSIS

Testing begins : DIAGNOSIS

- ✓ testing serum ceruloplasmin level
- ✓ ocular slit-lamp examination
- ✓ 24-hour urinary copper excretion


Obtain serum ceruloplasmin concentration*, an ocular slit-lamp examination, and 24-hour urinary copper excretion
Serum ceruloplasmin
<20 mg/dL (200 mg/L)
≥20 mg/dL (200 mg/L)
Kayser-Fleischer rings
Kayser-Fleischer rings
Absent
Present
Absent
Present¶
24-hour urine copper
24-hour urine copper
24-hour urine copper
>100 mcg (1.6 micromol)
≤100 mcg (1.6 micromol)
≤40 mcg (0.64 micromol)Δ
>40 mcg (0.64 micromol)
≤40 mcg (0.64 micromol)Δ
>40 mcg (0.64 micromol)
Diagnosis established
Obtain liver biopsy◇ or molecular genetic testing for ATP7B§
Diagnosis established
Wilson disease excluded
Obtain liver biopsy◇ or molecular genetic testing for ATP7B§

liver biopsy

On liver biopsy, a diagnosis of Wilson disease is established if the hepatic copper concentration is ≥250 mcg/g dry weight;

a diagnosis is excluded if the hepatic copper concentration is <50 mcg/g dry weight;

if the hepatic copper concentration is ≥50 and <250 mcg/g dry weight,

molecular genetic testing for mutations in ATP7B should be performed (if not already done) to establish or exclude the diagnosis.

Cancer risk

Patients with Wilson disease, especially those with cirrhosis, are probably at increased risk for hepatocellular carcinoma (HCC).

Progression of disease

Untreated, Wilson disease is universally fatal

Survival

The prognosis for patients who receive and are adherent to treatment for Wilson disease is excellent, even in some who already have advanced liver disease.

In patients without advanced liver disease, life expectancy is normal

Screening family members

Molecular genetic testing

Treatment

MEDICATIONS — two phases:

removing or detoxifying the tissue copper that has accumulated preventing reaccumulation.

potent chelators

D-penicillamine. However, approximately 30 percent of patients do not tolerate long-term therapy because of side effects and it may not be the treatment of choice in patients with neurologic symptoms.

Trientine has traditionally been used as a second-line agent for those intolerant of D-penicillamine,

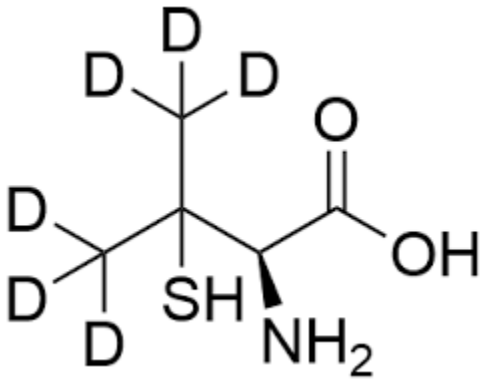
but it is also a reasonable option for primary therapy,

and may be the preferred treatment because of its lower incidence of side effects.

D-penicillamine

Dosing — The drug should be introduced at a dose of 250 to 500 mg/day and then increased by 250 mg increments every four to seven days to a maximum of 1000 to 1500 mg daily in two to four divided doses

should ideally be given one hour before or two hours after meals since food interferes with its absorption



Clinical improvement in patients with advanced liver disease is usually observed during the first two to six months of therapy,

but can continue thereafter.

Even advanced fibrosis or cirrhosis may show reversibility following prolonged treatment

Adverse effects

- Renal disease
- Severe thrombocytopenia
- Autoimmune tendency
- Nausea, vomiting, and anorexia
- Aplastic anemia
- Neurologic status of patients with predominantly neurologic symptoms may worsen

Monitoring D-penicillamine therapy

24-hour urinary copper repeatedly in the range of 200 to 500 mcg (3 to 8 micromol) per day on treatment. Most patients require at least six months to a year of chelation therapy to achieve these goals.

Maintenance therapy

patients should be clinically well

Normal, or near normal serum aminotransferases

Hepatic synthetic function

24-hour urinary copper repeatedly in the range of 200 to 500 mcg (3 to 8 micromol) per day

Trientine

another copper chelator, has been used successfully in patients unable to tolerate D-penicillamine as well as for primary therapy

250 mg, given in two or three divided doses. Similar dosing is used for adults (20 mg per kg), but the total dose should not exceed 1500 mg per day.

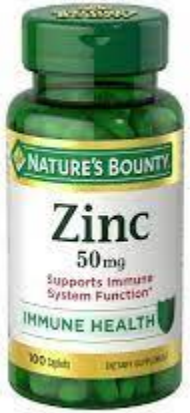
Adverse effects

- Hypersensitivity reactions and pancytopenia are rare.
- Neurologic worsening
- Hemorrhagic gastritis, loss of taste, and a rash

Oral zinc

Dosing is in milligrams of elemental zinc.

The dose of zinc acetate in adults and older children is a total of 150 mg zinc daily given in three divided doses



zinc in the treatment of Wilson disease has been in the care of patients during maintenance phases following treatment with a chelator .

However, it has also been used as primary therapy, in patients who developed worsening neurologic symptoms with D-penicillamine,

during pregnancy, and in young children

Most clinicians still rely on D-penicillamine or trientine as primary therapy for symptomatic patients.

Zinc is an alternative for patients who cannot tolerate these treatments,

who have neuropsychiatric disease that is not responding,

or for maintenance in those who have achieved therapeutic goals on chelation therapy

DIETARY RECOMMENDATIONS

During the initial phase of treatment, patients should avoid consuming food with high copper content,

in particular

shellfish, nuts, chocolate, mushrooms, and organ meats.

LOW COPPER DIET

1. Avoid:
2. Mushrooms
3. Nuts, Chocolate, Dried Fruit
4. Shellfish
5. Liver

Liver transplantation

curative for Wilson disease, and patients do not require treatment for Wilson disease following transplantation.

Outcomes for liver transplantation for Wilson disease are excellent .

Thank you for attention