WILSON DISEASE

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- Wilson’s disease is an autosomal recessive genetic

disorder of copper metabolism

- estimated prevalenceof approximately 1:30,000
- mutations in the ATP7B

WILSON DISEASE

- **progressive toxic accumulation of copper in the liver begins in infancy**
- **Deposition of copper in other organs, such as the nervous system, corneas, kidneys, and heart during the second decade or later**

WILSON DISEASE

- ESPGHAN Hepatology Committee:
- systematic reviews, prospective, and retrospective cohort or controlled studies from 1986 to 2016 in children <18 years
- Published in 2018


WILSON'S DISEASE
CNS disorders
Kayser-Fleischer ring
Hepatomegaly
Cardiomyopathy
Renal tubular dysfunction
Arthritis
Copper accumulates in tissues

Clinical presentations:

Hepatic >2 y

- Incidental finding of increased serum transaminases
- Acute hepatitis
- Hepatomegaly
- Fatty liver
- Acute liver failure with hemolysis
- Portal hypertension: esophageal varices, splenomegaly, low platelet count
- Decompensated cirrhosis with ascites

Clinical presentations:

- **WD** should be considered in the differential diagnosis of children **older than 1 year** presenting with any sign of liver disease ranging from

asymptomatically increased serum transaminases to cirrhosis with hepatosplenomegaly and ascites

or ALF

Clinical presentations:

Neurological and psychiatric Usually >15 y

- Dysarthria Case reports 7–9 y
- Dysphagia, excessive salivation
- Mood/behavior changes including depression, irritability
- Incoordination (eg, handwriting deterioration)
- Declining performance at school
- Resting and intention tremors
- Gait disturbance, dystonia, rigidity
- Mask-like face, risus sardonicus,
- Stroke-like symptoms

Clinical presentations:

- **Ophthalmic** >10 y : KF rings at slit lamp examination
- **Haematological** > 7 years :

  Acute/chronic hemolytic anemia
- **Renal** :

  Renal tubular dysfunction (Fanconi syndrome, tubular acidosis, aminoaciduria)

  Nephrolithiasis

  Nephrocalcinosis
- **Cardiac** :

  Cardiomyopathy, subclinical dysfunction

  Arrhythmia

Clinical presentations:

- **Endocrine**

  Hypoparathyroidism
- **Pancreatitis**
- **Skin lipomas**
- **Skeletal**

  Rickets/osteopenia/osteoporosis

  Arthropathy

Clinical presentations:

- **WD** may present at **any age** between **3 and 74** years

- The finding of **another possible cause** of liver dysfunction,
  - Acute viral hepatitis A
  - Nonalcoholic fatty liver disease
  - Nonalcoholic steatohepatitis
  - Autoimmune hepatitis

shouldnot exclude WD

Clinical presentations:

Neurological/psychiatric symptoms may occasionally be seen before 10 years of age:

- Mild cognitive impairment
- working memory
- language difficulties

Kayser-Fleischer rings :

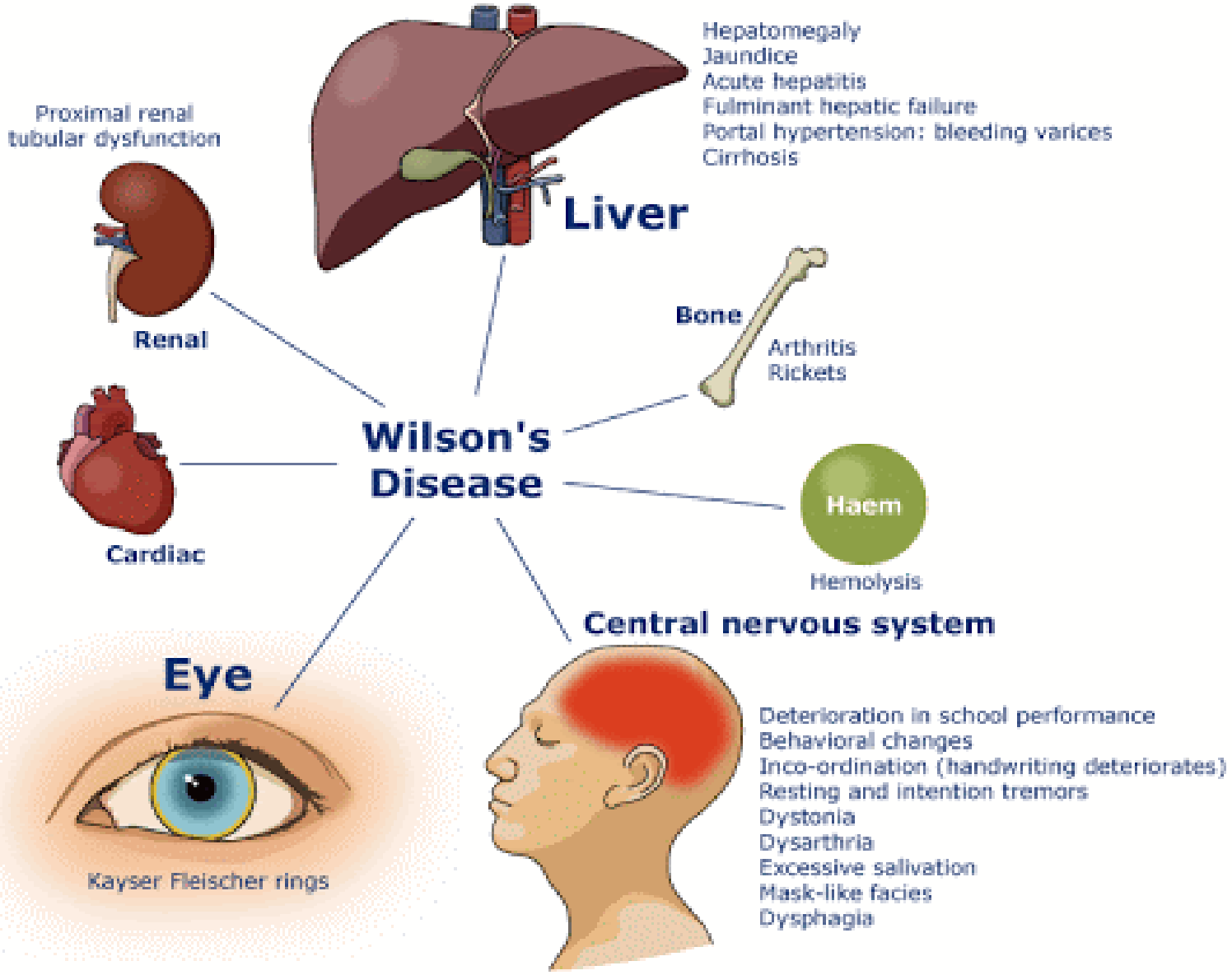
Are usually not seen in children with asymptomatic or mild liver disease,

but are **almost always** present in children with **neurological involvement**

Clinical presentations:

Acute hemolysis

- As the initial presentation of WD
- precipitated by infection or drugs
- Prominent in **fulminant** WD
- Average onset of 12.6 years


Hepatomegaly
Jaundice
Acute hepatitis
Fulminant hepatic failure
Portal hypertension: bleeding varices
Cirrhosis
Liver
Proximal renal tubular dysfunction
Renal
Bone
Arthritis
Rickets
Wilson's Disease
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

Diagnosis:

- Liver Function Tests
- Ceruloplasmin
- Total Serum Copper
- Urinary Copper Excretion
- Mutation Analysis
- Liver Biopsy

Diagnosis:

TABLE 3. Explorations of copper metabolism

	Normal values	High suspicion of WD
Serum ceruloplasmin	20–40 mg/dL	<10 mg/dL
24-Hour urinary copper excretion	<40 µg (<0.65 µmol)	>100 µg (1.6 µmol)
Liver copper content	<50 µg/g dry weight	>250 µg/g dry weight (>4 µmol/g dry weight)

Wilson Disease scoring System

TABLE 4. Diagnostic score in Wilson's disease, agreed at a consensus meeting (64)

Score	−1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms suggestive of WD (or typical brain MRI)		Absent		Present	
Coombs negative hemolytic anemia + high serum copper		Absent	Present		
Urinary copper (in the absence of acute hepatitis)		Normal	1–2 × ULN	>2 × ULN, or normal but >5 × ULN 1 day after challenge with 2 × 0.5 g D-penicillamine	
Liver copper quantitative	Normal		<5 × ULN (<250 μg/g)	>5 × ULN (>250 μg/g)	
Rhodanine positive hepatocytes (only if quantitative Cu measurement is not available)		Absent	Present		
Serum ceruloplasmin (nephelometric assay)		>0.2 g/L	0.1–0.2 g/L	<0.1 g/L	
Disease-causing mutations detected		None	1		2

Assessment of the Wilson's disease diagnostic score

0–1: Unlikely	2–3:Probable	4 or more: highly likely

A 6 y.o boy refer for high liver enzymes.He has Coombs negative hemolytic anemia, serum ceruloplasmin :0.02 g/L,normal slit-lamp examination and urinary copper:1200 mg /day.What is your idea about Wilson Dx in this patient?

- A. Unlikely
- B . Probable
- C. Highly likely
- D .Impossible

The Importance of Family Screening for Wilson's Disease

- screening first-degree relatives is recommended by both **European** and **American** guidelines

  Assessment include:
- physical examination
- serum ceruloplasmin
- liver function tests
- Urinary Copper Excretion
- molecular testing for ATP7B mutations
- **Newborn screening** is not warranted and screening may be delayed **until 1 to 2 years** of age.

Treatment

Chelating agents :

- **D-penicillamine**
- **Trientine**

Blocking the intestinal copper absorption : **Zinc salts**

Dietary copper **restriction** ??

- Avoiding copper-rich food (shellfish, nuts,

chocolate, mushrooms, and organ meats) is advised **until remission**

Treatment

- Treatment is **life-long**
- Monitoring of compliance
- Early detection of complications
- **Prognosis is excellent** provided **compliance** to therapy is adequate.

D-penicillamine

- Introduced in 1956
- Remains the **standard** treatment for WD
- **Chelates** copper ,**urinary** excretion
- Experimentally, also has a copper "**detoxifying**" effect inducing hepatic **metallothionein**
- D-penicillamine has been shown to efficiently prevent the progression of disease in **asymptomatic** children.
- Significant adverse effects resulting in drug withdrawal in up to **30%** of cases

D-penicillamine

- Sensitivity reactions:

  Fever , cutaneous eruptions,

  Neutropenia or thrombocytopenia, lymphadenopathy ,Proteinuria

- The medium- and long-term

  Lupus-like syndrome ,hematuria, proteinuria, arthralgia, bone marrow toxicity

- severe thrombocytopenia or aplasia
- skin changes related to D-penicillamine's anticollagen effects such as elastosis perforans serpiginosa, cutis laxa, pemphigus, lichen planus, and aphthous

stomatitis

- Elevations in serum antinuclear antibodies

Trientine

- Trientine, triethylene tetramine hydrochloride
- Was initially introduced in 1969 for WD who developed adverse events related to D-penicillamine

Rare reports of allergic reactions:

- Arthralgias
- Muscle cramps
- sideroblastic anemia

Trientine also chelates iron

Trientine

- **First-line** treatment with trientine :

Higher risk of **neurologic worsening** of symptomatic neurologic patients

Zinc salts

- First-line therapy for presymptomatic patients
- Maintenance therapy after initial decoppering
- Induction of metallothionein in enterocytes
- Copper absorbtion in the small intestine
- Induces hepatocyte metallothionein
- copper detoxifying effect
- Initiation of therapy with zinc salts presents also risk of neurological deterioration

Zinc salts

- Gastrointestinal symptoms : switching to zinc acetate.
- Anemia related to iron deficiency
- Increase of serum amylase and lipase (zinc containing enzymes)
- The recommended dosage :
- 25 mg twice daily children younger than 5 years
- older than 5 years of age :
- 75 mg/day (if body weight <50 kg)
- 150 mg/day (if body weight >50 kg) in 3 divided

TREATMENT

TABLE 5. Dosage and treatment monitoring

	Zinc salts	D-penicillamine	Trientine
Dosage in children	Zinc acetate, zinc sulphate Age >16 years and body weight >50 kg: 150 mg* day in 3 divided doses. Age 6–16 years and body weight <50 kg: 75 mg* day in 3 divided doses younger than 6 years of age:50 mg* day in 2 divided doses	Starting dose: 150–300 mg/day, gradually increasing once a week up to 20 mg/kg/day given in 2 or 3 divided doses or 1000 mg (max 1500 mg) in young adults given in 2 or 4 divided doses. Maintenance dose: 10–20 mg/kg/day up to 750 mg–1000 mg/day in 2 divided doses	Starting dose: 20 mg/kg/day or 1000 mg (max 1500 mg) in young adults given in 2 or 3 divided doses. Maintenance dose: 900–1500 mg/day in 2 or 3 divided doses.
Administration	1 hour before meal or 2 hours after meal	1 hour before meal or 2 hours after meal	1 hour before meal or 3 hours after meal
Adequacy of treatment parameters	Urinary copper excretion: 30–75 μg (0.5–1.2 μmol/L) /24 hours on maintenance treatment Serum zinc level >125 μg/dL Urinary zinc >2 mg/24 h on maintenance treatment	Urinary copper excretion: 200–500 μg (3–8 μmol/L)/24 hours on maintenance treatment	Urinary copper excretion: 200–500 μg (3–8 μmol/L)/24 hours on maintenance treatment
Liver function improvement	Usually 2–6 months, ALT normalization within 1 year	Usually 2–6 months	Usually 2–6 months
Indication for a drug change	Persistent ALT >3× upper limit of normal and/or INR >1.5 Poor tolerance, for example, nausea, abdominal pain, gastric ulcerations	Poor tolerance or side effects, for example, hypersensitivity reactions, fever, neutropenia, thrombocytopenia, lymphadenopathy or proteinuria	Poor tolerance or side effects, for example, allergic reactions, arthralgia, sideroblastic anemia

Treatment Strategy

- In asymptomatic children or children with mild liver symptoms : All available treatments
- In symptomatic patients:
- chelating agents (Dpenicillamine,trientine)
- Sequential treatment
- However under which conditions a patient can be switched to zinc maintenance ?

LIVE TRANSPLANTATION

- Indications :
- patients with ALF
- progression of liver dysfunction to liver failure despite drug therapy
- Decompensated cirrhosis
- Severe neurological disease
- Neurological and especially psychiatric involvement may show little improvement
- L.Tx cannot be considered for patients with severe neuropsychiatric involvement

LIVE TRANSPLANTATION

TABLE 6. Wilson's disease scoring system to predict the outcome of children with hepatic decompensation (King's Wilson index) by Dhawan et al (8)

Score	Bilirubin, μmol/L	INR	AST	Leukocytes, 10^9/L	Albumin, g/L
0	0–100	0–1.29	0–100	0–6.7	>45
1	101–150	1.3–1.6	101–150	6.8–8.3	34–44
2	151–200	1.7–1.9	151–200	8.4–10.3	25–33
3	201–300	2.0–2.4	201–300	10.4–15.3	21–24
4	>300	>2.5	>300	>15.3	0–20

A 12 y.o girl known case of Wilson Dx has Bilirubin=210 mmol/L,INR=2.8, AST=250,Leukocytes=5.4*10^9/L and Albumin g/L .What is your plan of therapy?

A. D-penicillamine with zinc

B. Trientine with zinc

C. D-penicillamine with trientine

D. Start D-penicillamine and consider liver TX

Monitoring

- P/E
- LFT
- 24 hours urinary copper
- Yearly slit-lamp examination
- Brain MRI

Initiation of therapy :

- Every 1 to 3 months until remission and every 3 to 6 months afterwards.
- Non adherence : life-threatening deterioration
- Intervals should be shorter in adolescents


Thank for your attention