EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL-ERN Clinical Practice Guidelines on Wilson's disease☆

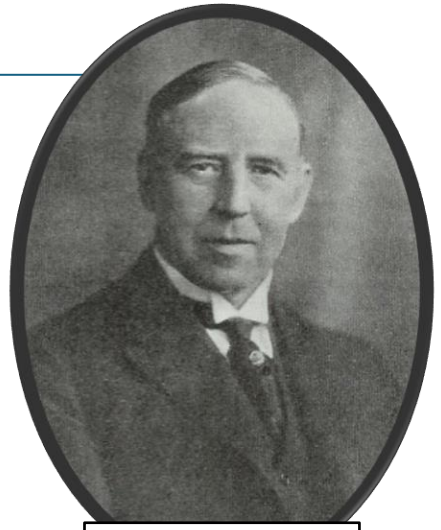
Dr Manel Moalla
Gastroenterologist
Hedi Chaker Hospital, Sfax

Journal of Hepatology, **April 2025**

Introduction

- **Rare autosomal recessive** disorder of copper metabolism
- Due to mutations on **both alleles of ATP7B** leading to :

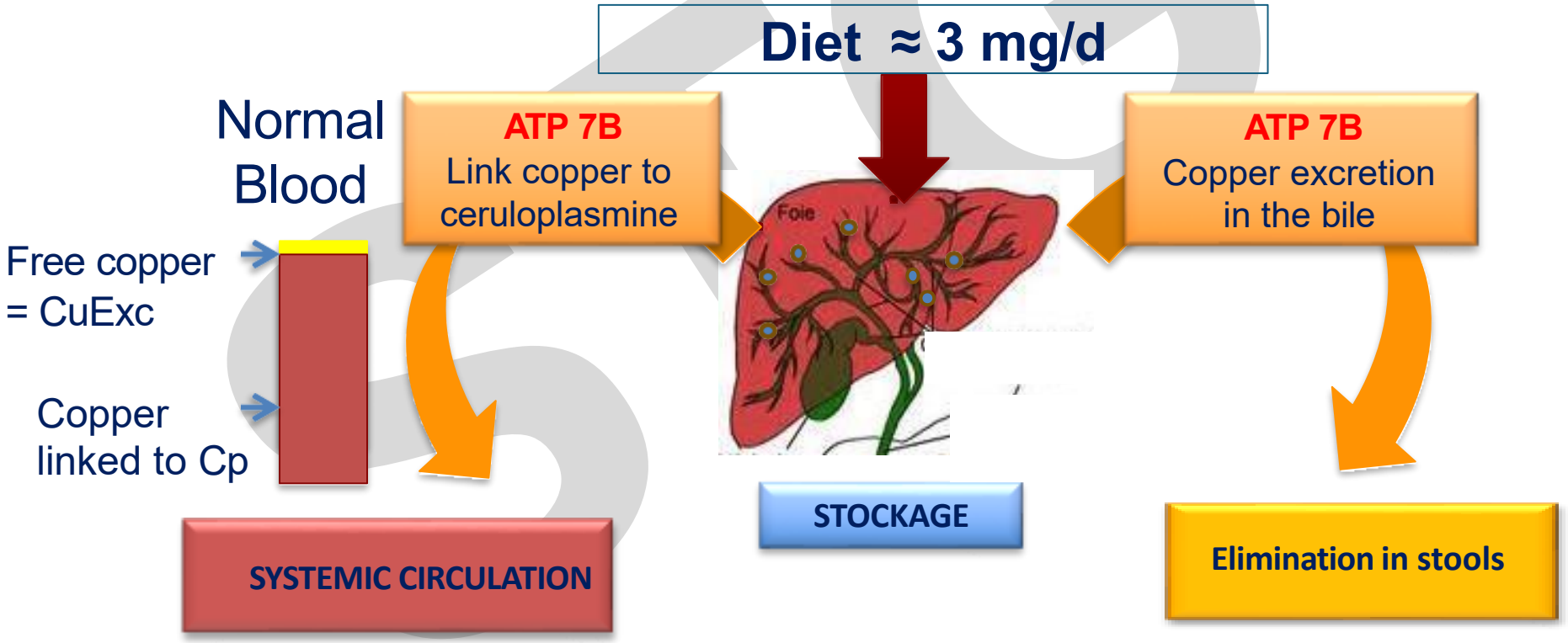
➔**copper accumulation** in the liver, brain and other body organs



WILSON
1878-1937

Physiopathology

ATP7B gene coding for **ATPase 7B** :
main regulator of cellular copper metabolism

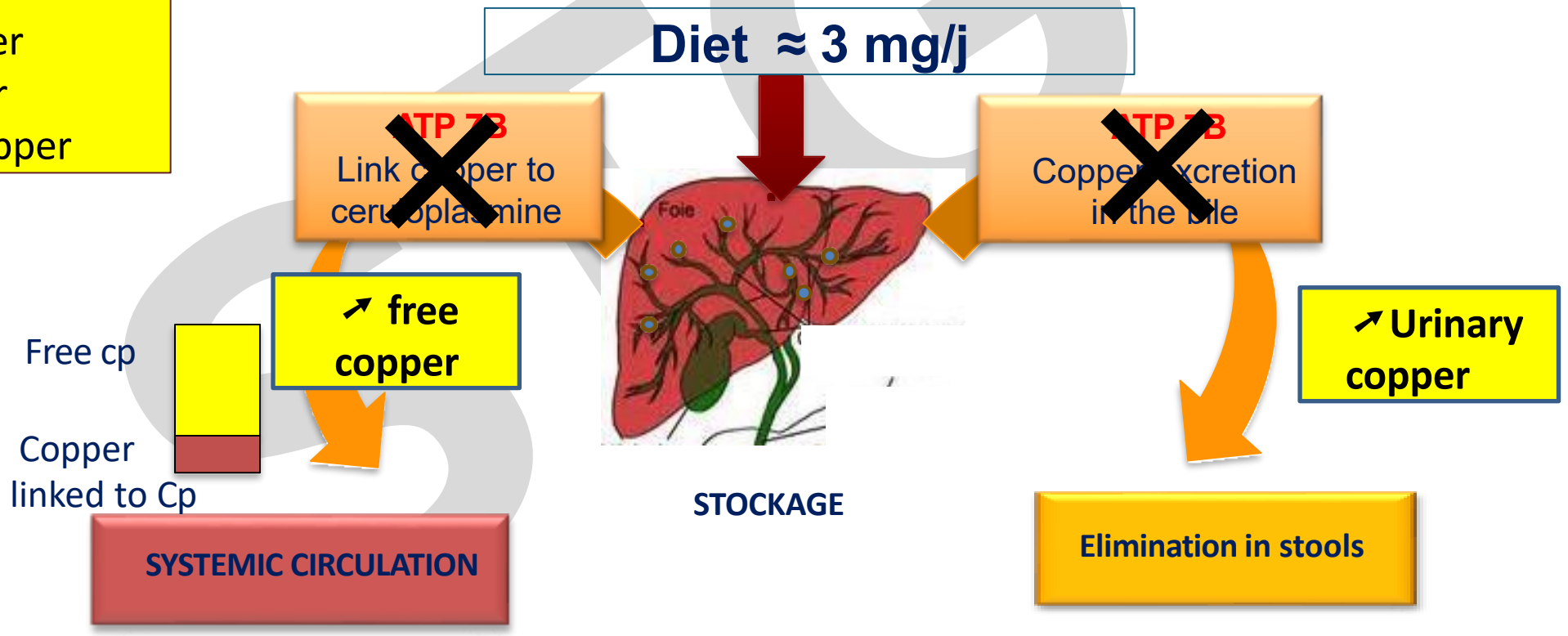


Physiopathology

Homozygous mutation on **ATP7B : non functional ATPase 7B**

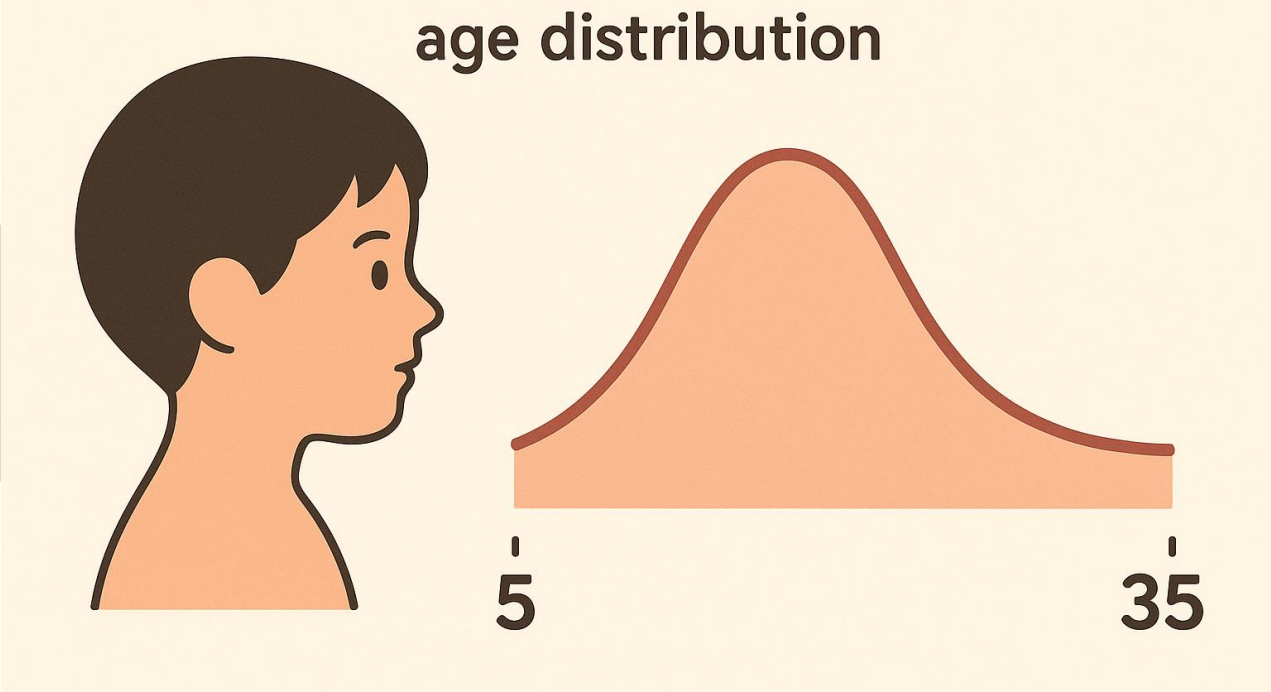
↘↘ functional Cp

↘ Total copper
↗ Free copper
↗ Urinary copper

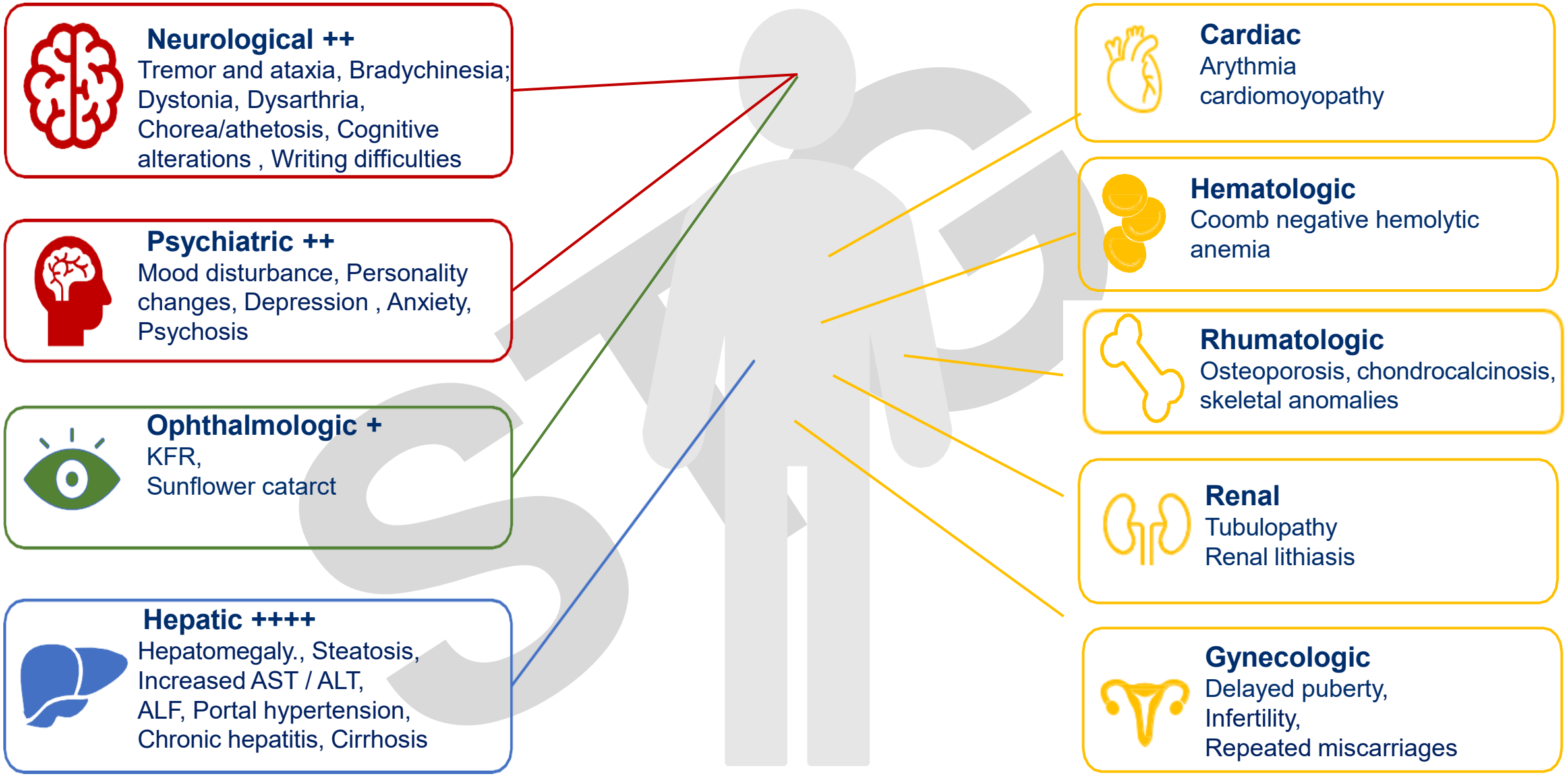


Age of presentation

- May present at any age
- **Majority between 5 and 35 years of age**



Clinical presentation



Liver presentation :

most frequent presentation : 49%

Any severity of liver disease may be encountered

Asymptomatic with increased transaminases or steatosis

Acute hepatitis

Auto-immune like hepatitis (30%)

Acute liver failure (ALF) 5%

Young female +++

Suspect WD if ALF with:

1) mildly increased transa
2) Severe jaundice
3) hemolysis

Chronic hepatitis Cirrhosis+++

Neurological presentation

- Symptoms usually start at 20-30 years of age : **10 years after the onset of liver disease**

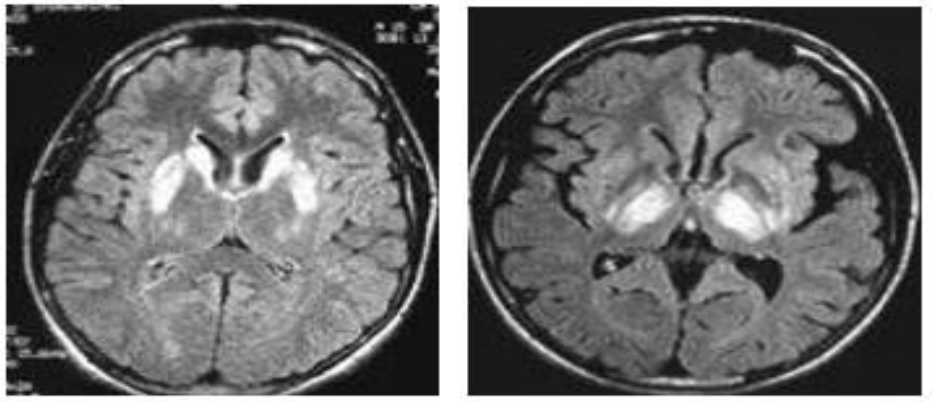
3 syndrome types:

Tremor and ataxia

Bradykinesia : parkinsonism-like

Dystonia

- In many cases, neurological symptoms are very difficult to classify
- Brain-MRI is always abnormal

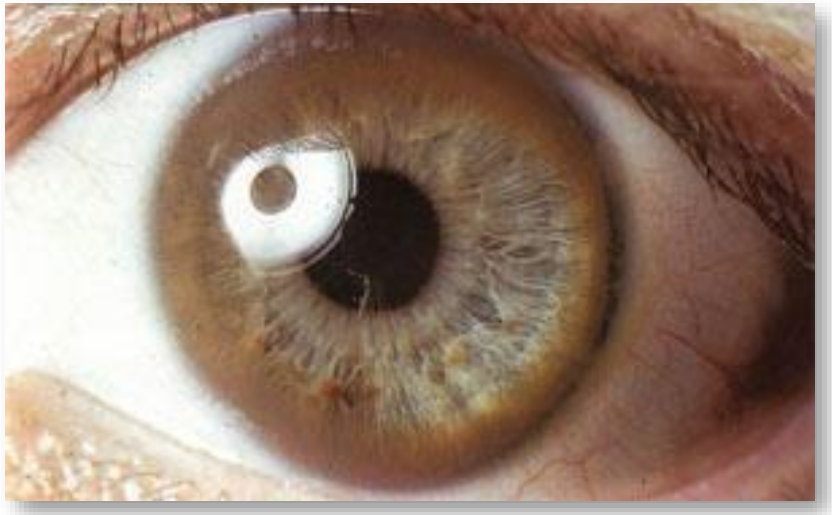


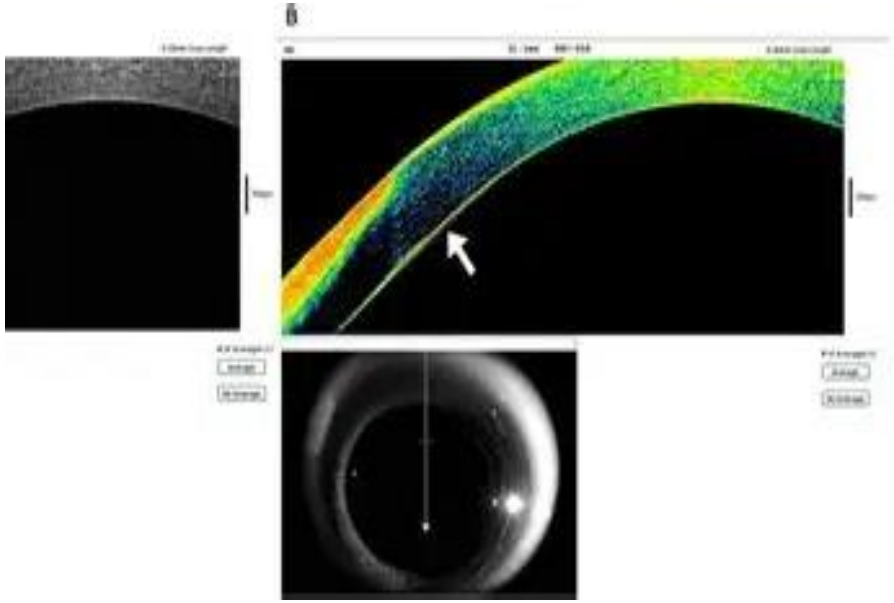
Ophtalmological signs:

Kayser-Fleischer ring : the clinical hallmark of WD

- Present in **95%** of patients with **neurological signs** and ≈ 50% of those without neurological signs

- **Not entirely specific for WD**: may be found in patients with chronic cholestatic diseases





It is detected using:

- **Slit lamp examination**
- or **Optical coherence tomography (OCT)** (new)

Which diagnostic approach in **predominantly hepatic presentation?**

Diagnostic approach in **predominantly hepatic presentation?**

- **Typical features of WD:** KFR, neurological signs, Brain MRI, hemolytic anemia

• **Copper analysis:**		**High suspicion of Wilson's disease**
➢ Serum ceruloplasmin	↘	**<10 mg/dl**
➢ 24-h urinary copper excretion	↗	**>100 µg /24 h**
➢ REC (Relative exchangeable copper) (new)	↗	**>15%**

REC:

New biological marker since 2009

- **REC > 15%:** Sensitivity and specificity close to **100%**
- **CuExc > 2.08 µmol/L : predict extrahepatic involvement and its severity**

➔ **Diagnostic et prognostic value**

Which diagnostic approach in **predominantly hepatic presentation?**

- **Typical features of WD:** KFR, neurological signs, Brain MRI, hemolytic anemia

- **Copper analysis:**
  - Serum ceruloplasmin
  - Basal 24h urinary copper
  - REC (relative exchangeable copper) if available

- **Genetic ATB7B analysis** → confirm diagnosis + family screening

- **Hepatic parenchymal copper quantification** (dry weight) if diagnosis remains uncertain (>250 µg/g highly suggestive)

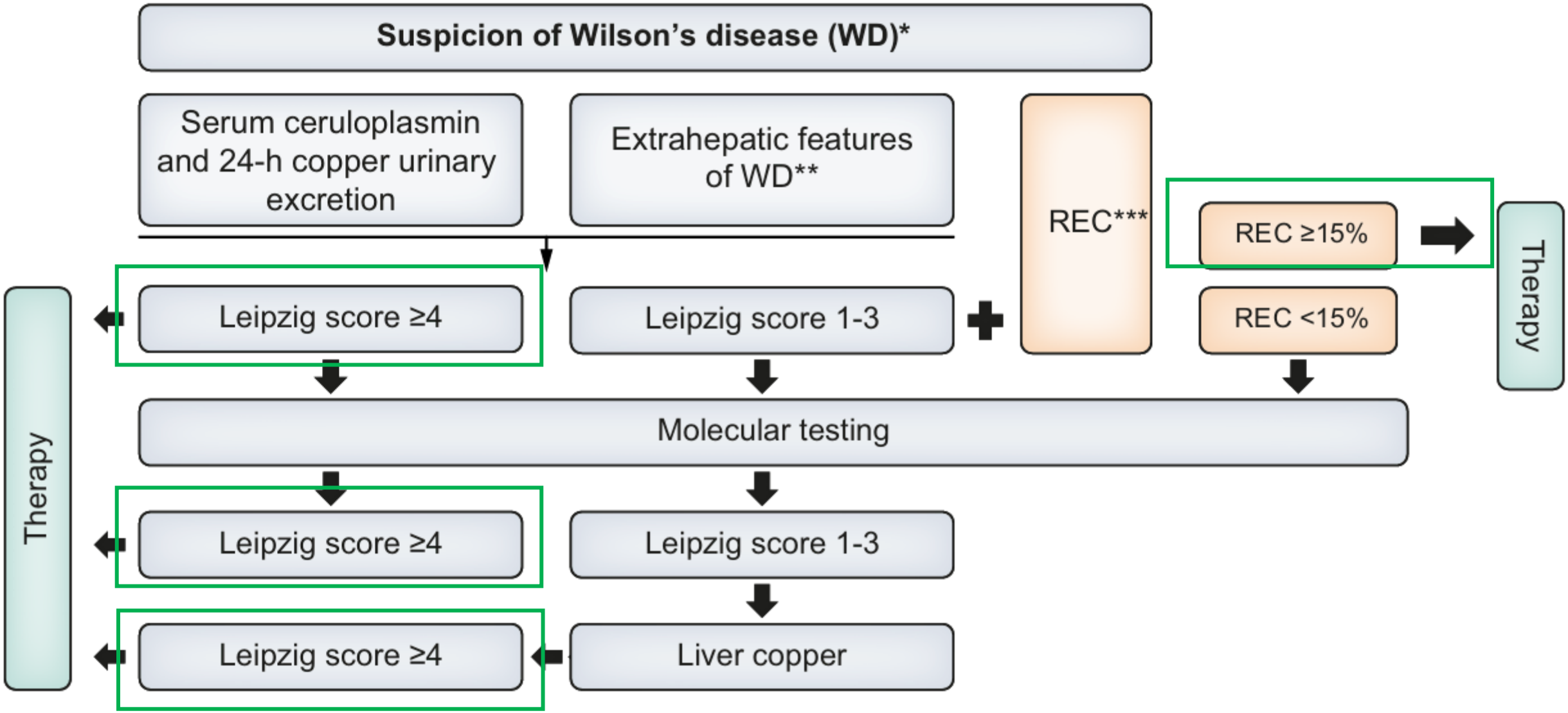
Diagnostic Leipzig score in Wilson's disease

Score	-1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms (or typical brain MRI)		Absent		Present	
Coombs-negative haemolytic anaemia + high serum copper		Absent	Present		
24-h urinary copper excretion (in the absence of acute hepatitis)		Normal	1-2 x ULN	>2x ULN	
Serum ceruloplasmin		>0.2 g/L	0.1- 0.2 g/L	<0.1 g/L	
Rhodanine positive hepatocytes (Only if quantitative copper measurement is not available)		Absent	Present		
Liver copper quantification	Normal		<250 ug/g	>250 ug/g	
Detected mutations		None	1		2

0-1: unlikely **2-3: probable** **≥ 4 : highly likely**

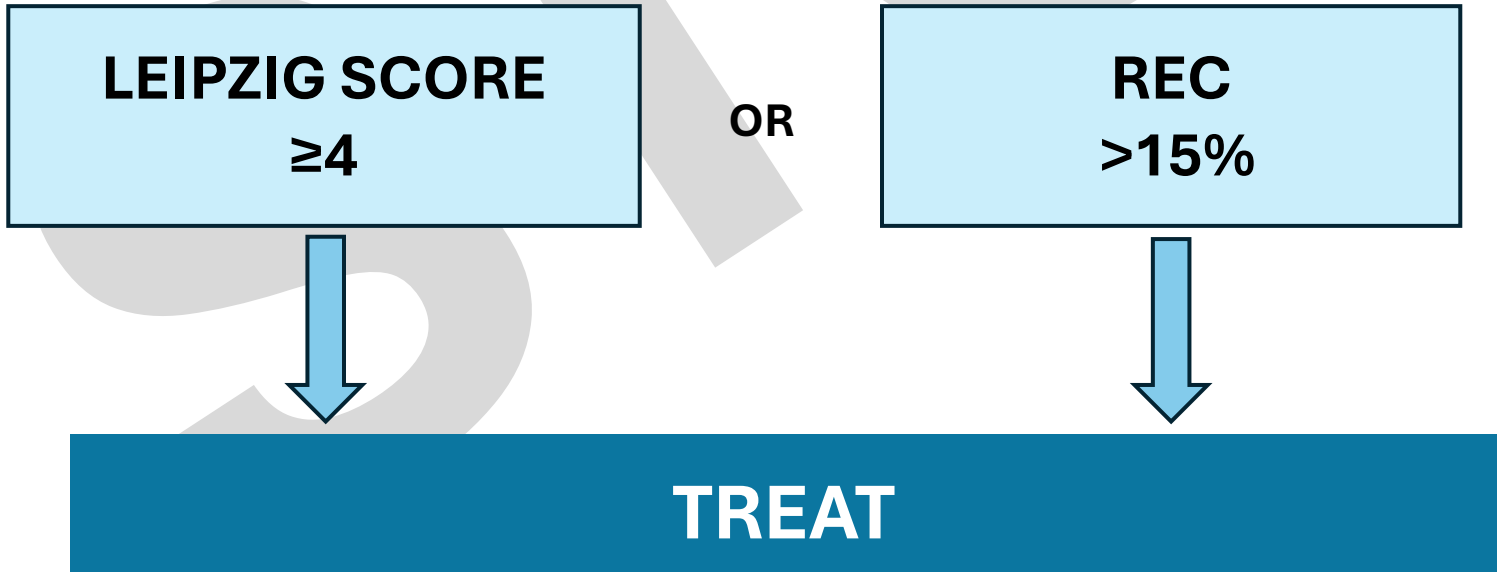
Ferenci P. Liver Int. 2003

Diagnostic algorithm according to Leipzig score (changed)



Treatment

- Pharmacological treatment should be started once diagnosis is well supported by the Leipzig score **(LoE 2, strong recommendation, consensus).**

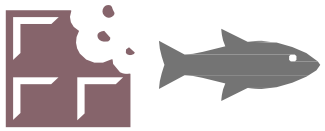


Treatment

Pharmacological treatment

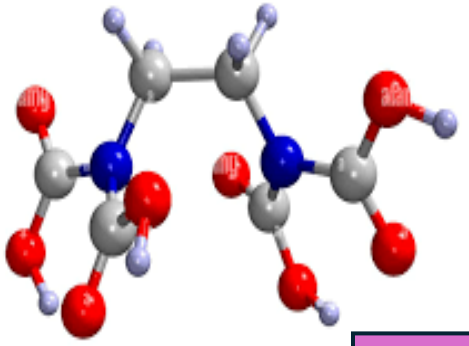
- ✓ Specific
- ✓ No specific

Low copper diet

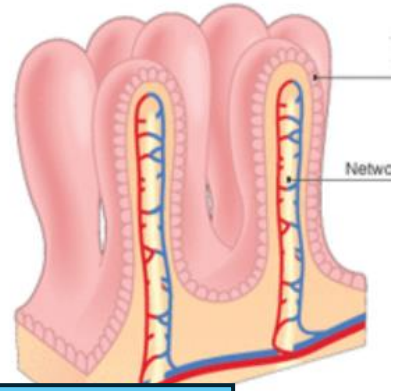


Liver transplantation

Specific pharmacological treatment



TWO MECANISMS:



CHELATORS:
↑↑ Urinary excretion

INHIBITERS OF INTESTINAL COPPER ABSORPTION
↓↓

- D-penicillamine
- Trientine
- Zinc salts

Specific pharmacological treatment

D-penicillamine

- **1st line** therapy in **symptomatic patients (all presentations)**

- **Starting dose: 1000 -1500 mg/d** given in 2 or 3 divided doses.
- **Maintenance dose: 750 -1000 mg/d** in 2 divided doses (new)
- **'start low, go slow'** Increases in dose should be progressive (8 weeks) : especially in patients with neurological presentation: start with 300mg /day (increase weekly or monthly)

- **The most toxic treatment:**

Early adverse effects :

✓sensitivity reactions

Medium- and long-term adverse events:

✓lupus-like syndrome

✓bone marrow toxicity

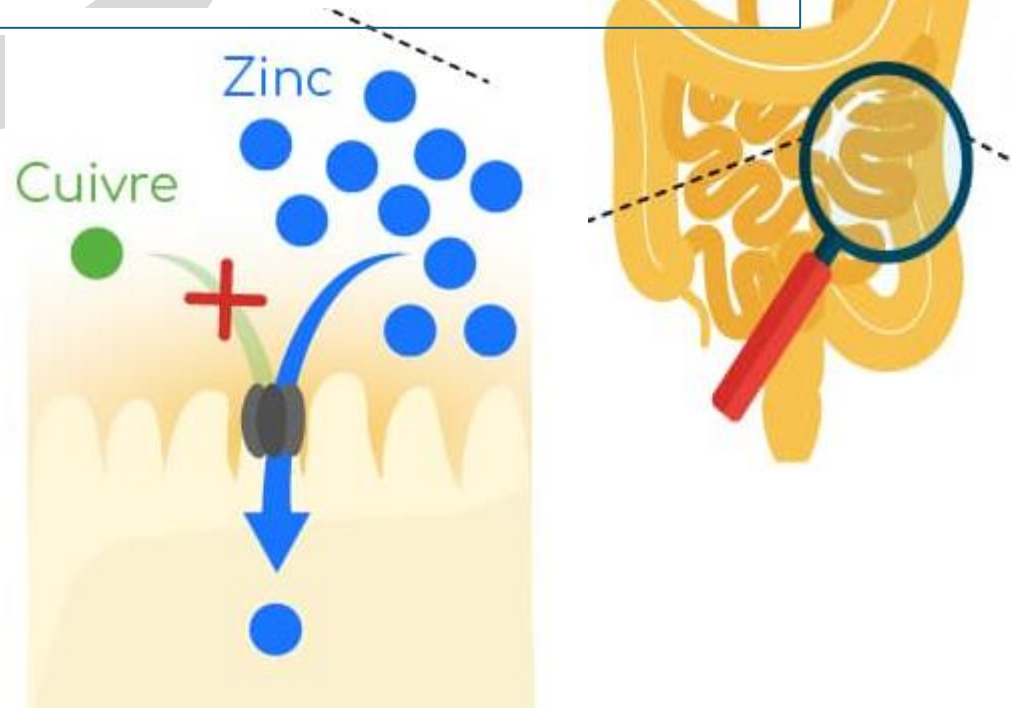
✓skin changes such as elastosis perforans serpiginosa, cutis laxa, pemphigus, lichen planus, and aphthous stomatitis

Specific pharmacological treatment

Zinc salt

- **1st line** therapy in **asymptomatic patients**
- **Maintenance therapy** after good response to chelators
- May be used in 1st line in neurological presentation

- **Dosage: 50 mg x 3 /d**



Specific pharmacological treatment

		Chelators		Zinc salts
		D-penicillamine	**Trientine**	**Zinc Acetate**
		Trolovol® 300mg	Cufence® (TN-2HCL) 200mg Cuprior® (TN-4HCL) 150 mg	Wilzin® 50mg
Mecanism	**Copper urinary excretion**	↗↗↗	↗↗	-
	Copper absorption	-	↘	↘↘↘
Dosage	**Starting dose : 8 weeks**	**1000 - 1500 mg/d (start with 300mg)**	TN-2HCL 750 à 1600 mg TN-4HCL 600 à 975 mg	**50 mg x 3 /d**
	Maintenance: life long	**750- 1000 mg/d(new)**	TN-2HCL 750 à 1500 mg TN-4HCL 450 à 975 mg	
		1h before meal or 2h after meal		
Indication		**-1st line: symptomatic forms**	- 2d line if side effects or non response - 1st line if penicillamin is contraindicated	**- 1st line: asymptomatic forms** - 2d line if side effects or non response
Side effects		**+++**	+	**+**

Low-copper diet (first year of therapy ++)

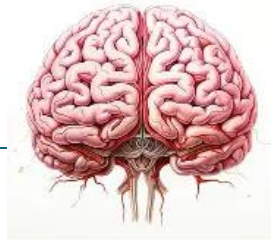
Patients should avoid:

- Shellfish
- Dark chocolate
- Lamb’s and beef’s liver
- Nuts
- Mushrooms

Non specific treatment :

Neurological symptoms :

- ✓Beta-blockers
- ✓Benzodiazepines
- ✓Dopamine agonists
- ✓Toxin botulinum injections
- ✓Physiotherapy, speech therapy
- ✓Neurosurgical procedures…



Psychiatric symptoms :

- ✓Antidepressant agents
- ✓Antipsychotics
- ✓Benzodiazepines
- ✓Lithium
- ✓Behavioural therapy..

Liver transplantation

Indications:

- ✓Acute liver failure
- ✓Decompensated cirrhosis
- ✓Severe neurological WD with no response to treatment (case by case)

Anti-copper therapy is not indicated after LT

Pregnancy and breastfeeding

Recommendation

- Any anti-copper therapy should be maintained during pregnancy and breastfeeding **(LoE 4, weak recommendation, consensus).**

Reduce the dose of copper-chelating agents during the 1st trimester

Follow up

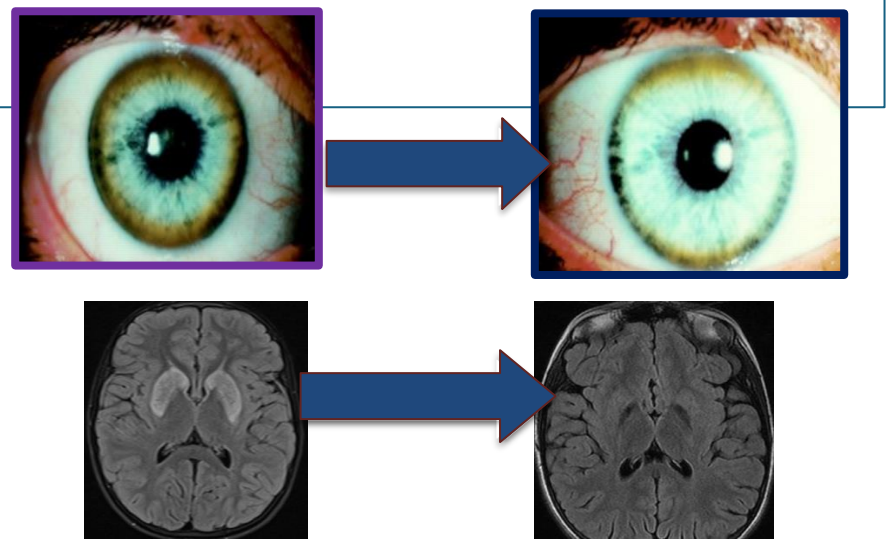
- **Clinical signs**
- **Biology**

- **Every 6 to 12 months**
- **More frequently if :** every 15 to 30 days
  - ✓ recently started treatment
  - ✓ decompensated cirrhosis
  - ✓ significant neurological disability

- **Ophtalmological exam**
- **Brain MRI**

Annual if abnormal initially

- **Liver US:** annual or semestrial (if cirrhosis)



Follow up

Chelators | **Zinc salt**

- ✓ Full blood count
- ✓ liver profile
- ✓ renal profile
- ✓ Coagulation profile
- ✓ 24 h urinary copper
- ✓ CuExc (if available)

- ✓ 24-h proteinuria (patient on D-P)
- ✓ Antinuclear antibodies

- ✓ Lipases (if abdominal pain)
- ✓ Lipid profile
- ✓ Serum zinc
- ✓ 24-h urinary zinc

Follow up

Adequacy of treatment on maintenance therapy:

24-h urinary copper excretion

Chelators

200–500 µg/ 24H

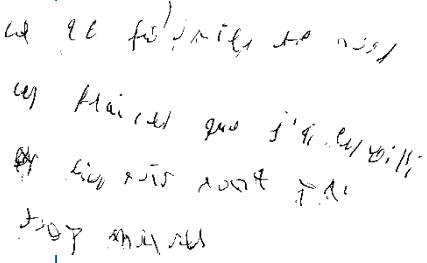
Zinc salt

30-75 µg/24 h

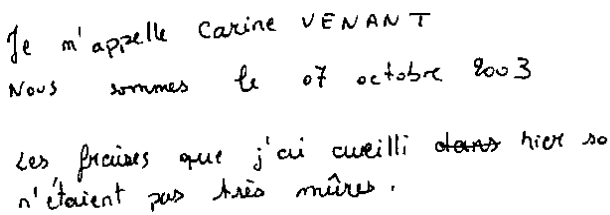
+ normal Exchangeable copper

Treatment response

- Defined by :
  - ✓ resolution or improvement of clinical signs
  - ✓and/or improvement of liver parameters (ALT, INR, albumin)
  - ✓or at least no deterioration on a validated scale or on brain imaging



3 years later



If not achieved : switch therapy :

- ➢ D-penicillamine to trientine and vice versa
- ➢ or zinc to chelators

Screening approach in first degree relatives

- Evaluate **clinical symptoms** and **liver tests**

- **Serum ceruloplasmin + 24h urinary copper excretion**

  (and REC if available)

- **Molecular-genetic testing** to search for the biallelic variants

Take home messages

THINK WILSON

- ✓ Wilson's disease presents usually **before the age of 40**
- ✓ Variable presentations : most common **hepatic** then **neuropsychiatric** presentation
- ✓ **Exchangeable copper and REC** are the new diagnostic and prognostic biomarkers
- ✓ The diagnosis must be confirmed by the detection of a **mutation in the gene ATP7B**
- ✓ **D-penicillamine** is the 1st line treatment for symptomatic forms
- ✓ **Zinc salts** are the 1st line treatment for asymptomatic forms
- ✓ **Perspectives: Gene therapy**: transduction of a new ATP7B to restore copper hepatic metabolism