Liver cirrhosis and neurologic disorders associated with Wilson disease (clinical case presentation).

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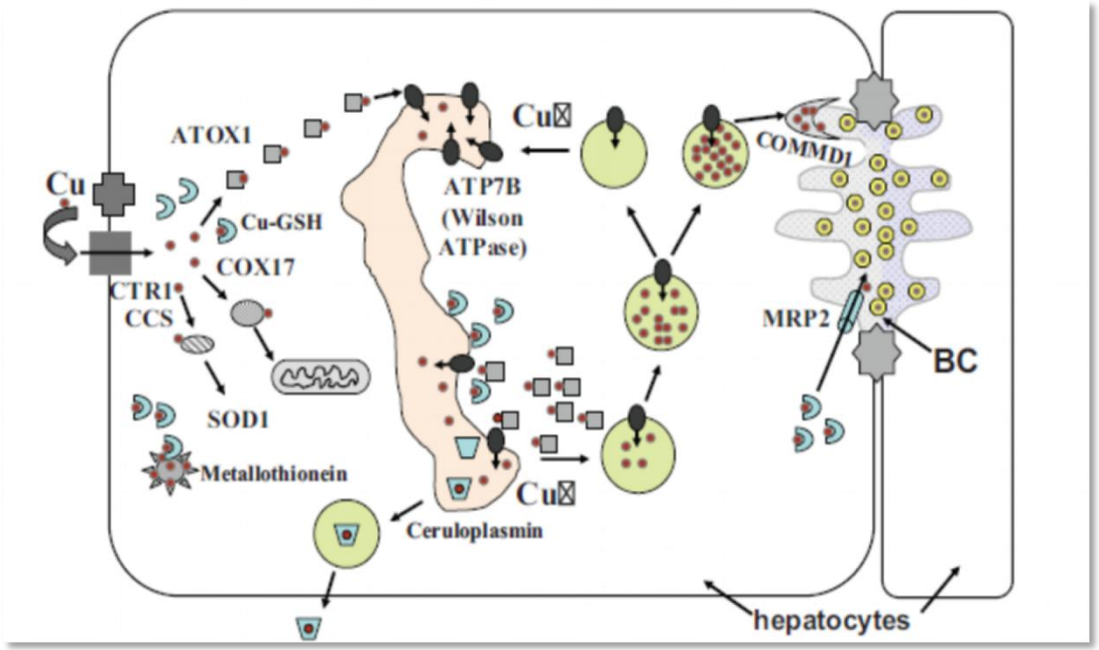
Almaty, 2024

Wilson Disease

Wilson’s disease is a progressive, inherited disorder in which defective biliary excretion of copper leads to its accumulation, particularly in liver and brain. Over time, the damage from the accumulation of copper results in the hepatic, neurologic, and psychiatric manifestations of Wilson disease.

EASL Clinical Practice Guidelines: Wilson’s disease European Association for the Study of the Liver, Journal of Hepatology, Volume 56, Issue 3, 671 - 685

Pathophysiology of Wilson Disease



Mutations of the ATP7B gene on chromosome 13

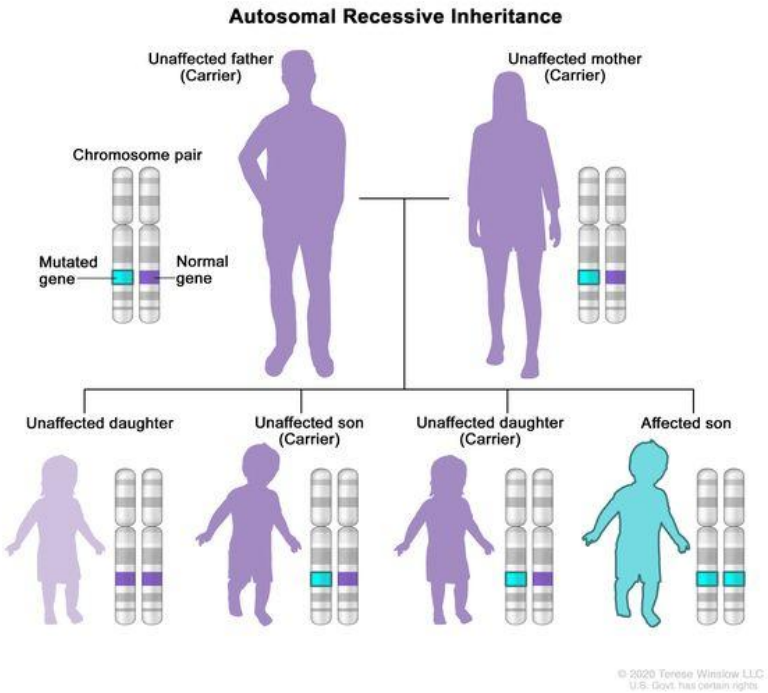
Impaired synthesis of transmembrane ATPase in hepatocytes

Defective intracellular copper transport in hepatocytes

•Elevation of “free” copper concentration and **systemic accumulation**

https://med-gen.ru/docs/disser_Bayazutdinova%20GM.pdf

Inheritance



In autosomal recessive inheritance, **both parents** must carry one copy of the defective gene to have a chance of passing it to their offspring.

- 25% of being affected by the disorder
- 50% probability of being an asymptomatic carrier
- 25% probability of being unaffected and non-carrier

https://webmedinfo.ru/bolezn-vilsona-konovalova.html

Epidemiology

Prevalence	• Orphan disease • *Orphanet:* 1-9 cases: 100,000 (on average, 1: 25,000) • European database: 1.2–1.8 cases: 100,000 • CIS countries: 0.3–1.0 cases: 100,000 • Higher in regions where there are **consanguineous marriages** (Iran, Yemen, Ireland, Japan, Sardinia)
Incidence	• 1: 30 000-100 000
Carrying the defective gene	• Every 90-100 (1%)
Gender and age	• Men and women equally • Average age of **onset is 11-25 years**

Федеральные клинические рекомендации по диагностике и лечению Болезни Вильсона-Коновалова (Гепатолентикулярная дегенерация). Москва-2015., профессор Асанов А.Ю., профессор Соколов А.А., профессор Волгина Маевская М.В., Ведерникова.В., Ивашкин В.Т. и др. Болезнь Вильсона (клиническое наблюдение). Российский журнал гастроэнтерологии, гепатологии и колопроктологии. 2002; (5): 20—2.
https://www.umj.com.ua/article/47843/epidemiologicheskie-i-kliniko-nevrologicheskie-aspekty-bolezni-vilsona-konovalova

Epidemiology in Kazakhstan (predicted model)

carry one copy of the defective gene - 1%

Population 20 million
1% = 200 000 people

The annual rate of detection of new cases is 1 per 30,000 population

600 patients

Family screening

If the heterozygous form, then the disease remains asymptomatic

Children
312 patients - 52%

Adults
288 patients - 48%

Pediatricians

Gastroenterologists

Neurologists

Therapists

Ophthalmologists

infectious disease specialists

Psychiatrists

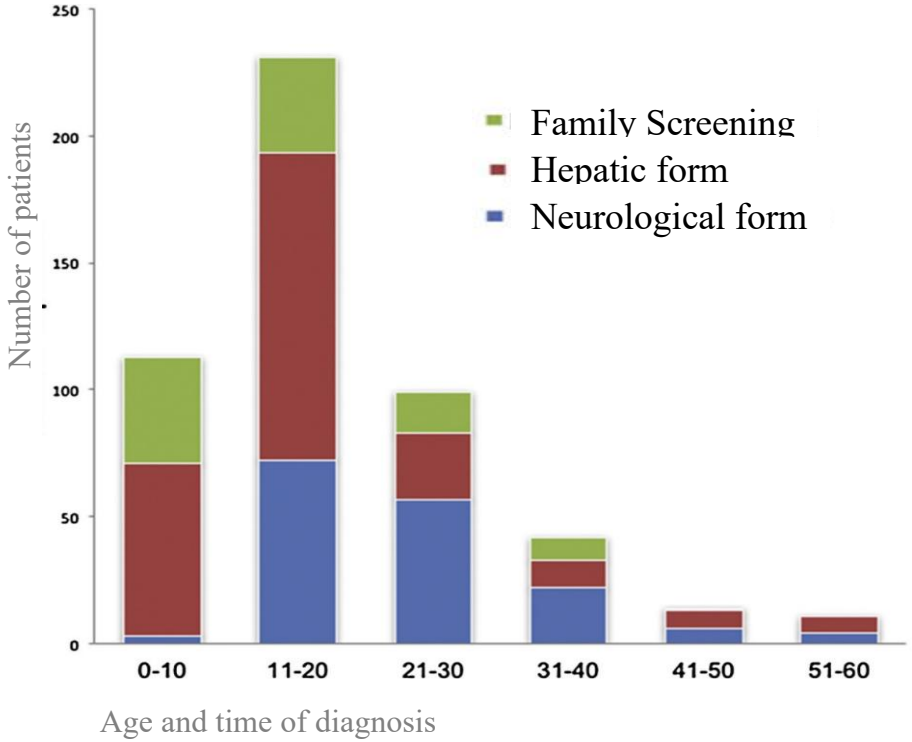
Hematologists

Family doctors

Clinical patterns (AASLD 2022)

Hepatic	• Asymptomatic hepatomegaly • Isolated splenomegaly • Persistently elevated serum aminotransferase activity (AST, ALT) • Fatty liver • Acute hepatitis, varying severity including acute liver injury (ALI) • Resembling autoimmune hepatitis • Cirrhosis—compensated or decompensated • Acute liver failure
Neurological	• Dysarthria • Movement disorders (tremor, involuntary movements) • Pseudobulbar palsy • Drooling, transfer dysphagia • Rigid dystonia • Dysautonomia • Seizures • Sleep disorders, insomnia
Psychiatric	• Depression • Bipolar disorder/bipolar spectrum • Neurotic behaviors • Personality changes • Psychosis
Other systems	• Eye: Kayser–Fleischer rings, sunflower cataracts • Renal abnormalities: aminoaciduria and nephrolithiasis • Skeletal abnormalities: premature osteoporosis and arthritis • Cardiomyopathy, dysrhythmias • Pancreatitis • Hypoparathyroidism • Infertility, repeated miscarriages

Age and phenotype in WD (French Register, n=604)



Age	• 51.6% were under the age of 16; 10% have the first symptoms after 30, 6.2% after 40 years
Form	• 47% - hepatic • 32,2% - neurological
Interval between first symptoms and Ds	• Hepatic - 14,4 month • Neurological- 44,4 month
Ds at screening	• 20,8%

https://www.sciencedirect.com/science/article/pii/S2210740118300469

Clinical Case

Clinical Case

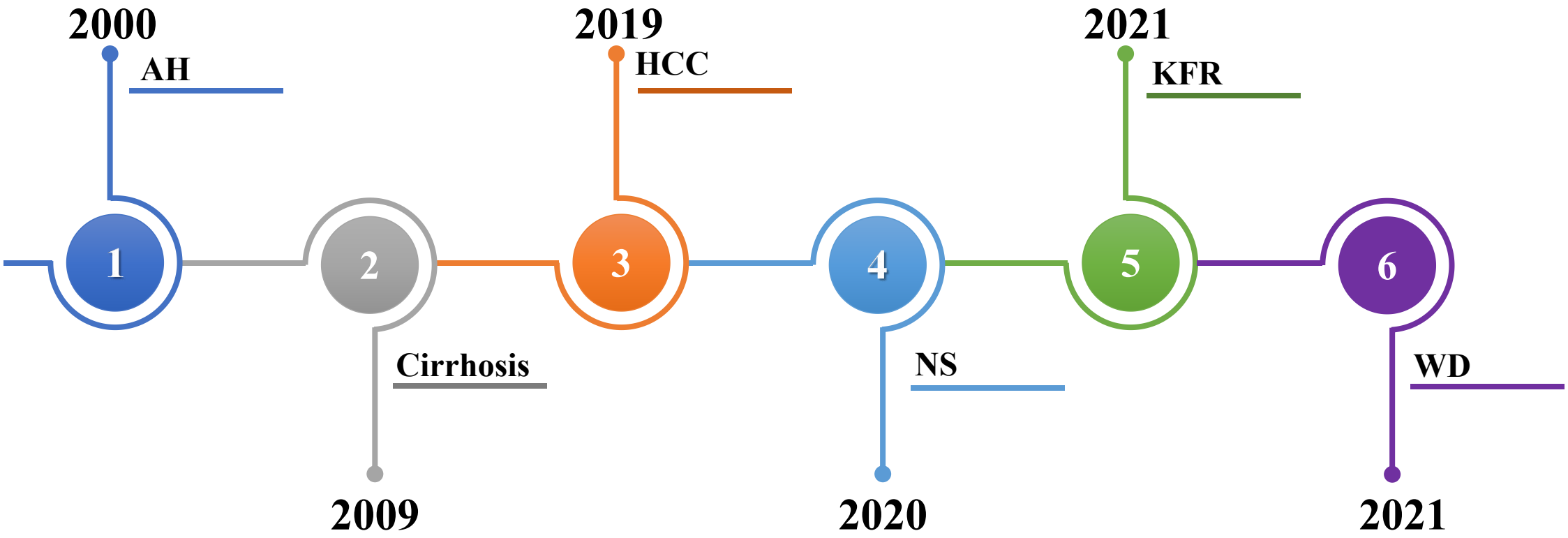
29 y.o., Man

Complaints: periodic discomfort in the right hypochondrium, abdominal bloating, dizziness, frequent syncope, hypoglycemia (1.3 mmol/l), paresthesia in the arms and legs, sometimes tremor

Anamnesis vitae

- Normal pregnancy reported
- Non-consanguineous marriage between parents
- No known allergies
- Diagnosed with Hepatitis A at age 3

Anamnesis morbi



Acute hepatitis

2000

AH

+ transfusion of RBC

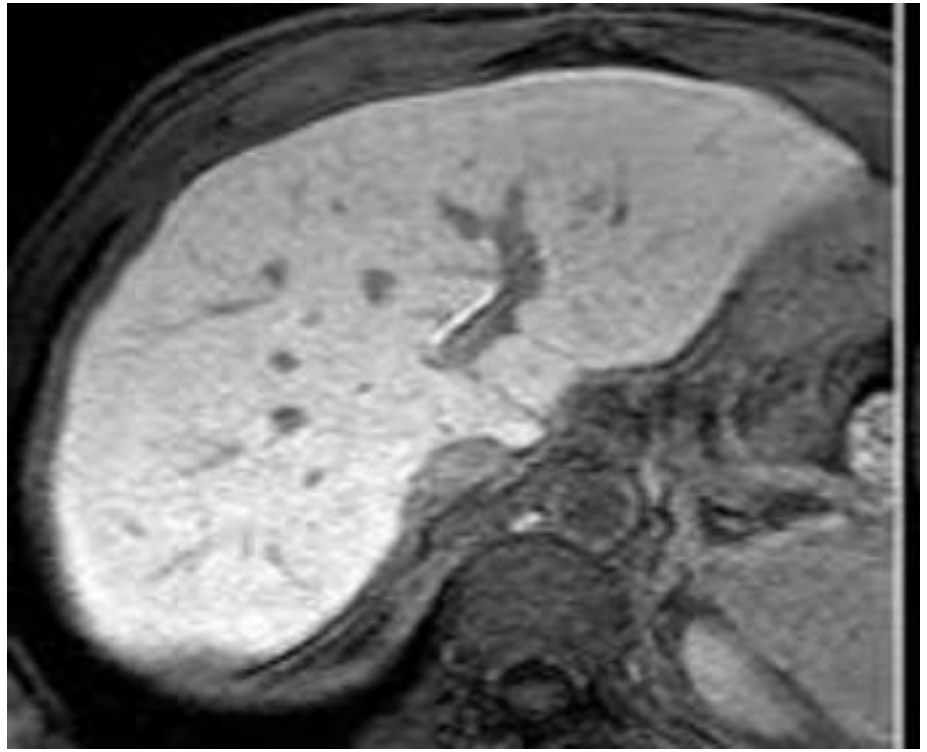
1

ALT, U/L	ACT, U/L	BIL µmol/l	HB, g/l
1820	1590	324	50

Hepatomegaly, periportal lymphadenopathy, splenomegaly, increased thickness of the gallbladder wall, decreased or increased echogenicity of the liver and increased echogenicity of the portal walls.

Cirrhosis

Esophageal varices 2 grade.



Contour abnormalities and parenchymal nodules of the liver.

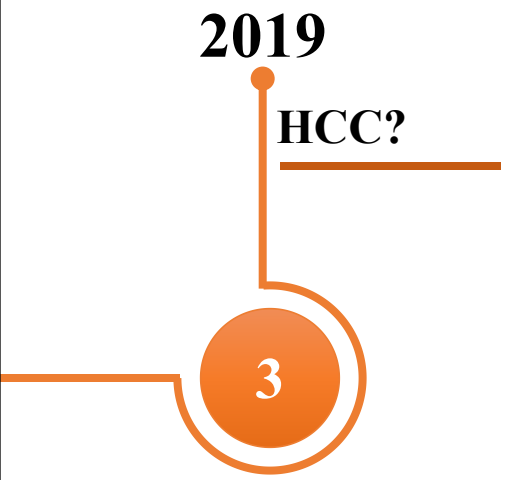
2

Cirrhosis

2009

ALT, U/L	ACT, U/L	BIL µmol/l	INR
44,9	37,4	24	1,4

Hepatocellular carcinoma?



Upon comparison with prior CT scans dated 16/10/2017 and 15/02/2019, the following findings are noted:

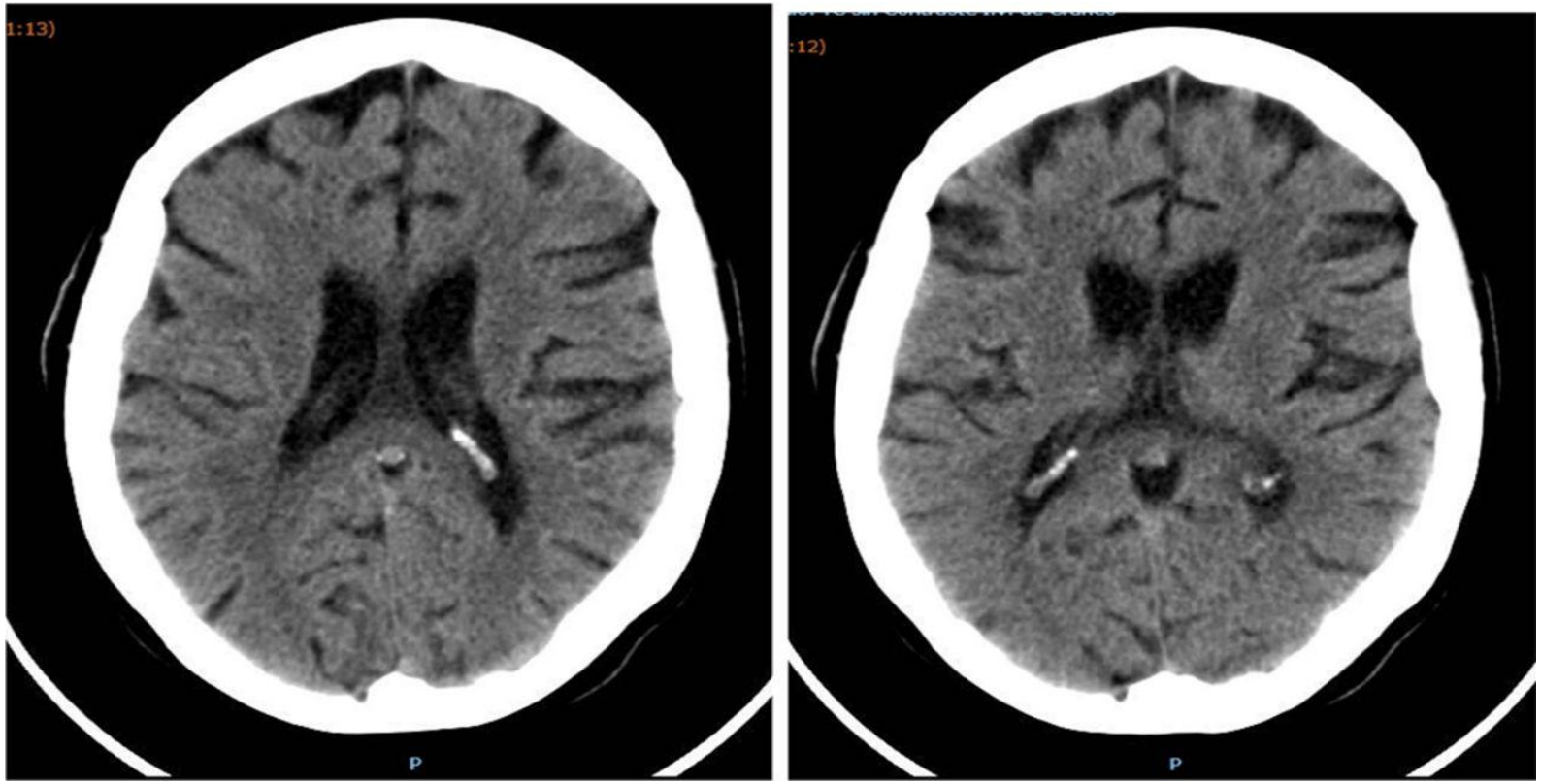
- Two contrast-enhancing lesions are observed in the 3rd segment of the liver. One lesion has **increased in size from 31 mm to 36 mm,** while the other remains stable at 6 mm.
- **Two additional formations are detected** in the 8th and 6th liver segments, measuring 10 mm and 8 mm, respectively.

These findings suggest **progression of the disease process**. Transformation into **hepatocellular carcinoma (HCC) cannot be excluded** and may warrant further evaluation.

Liver cirrhosis of mixed etiology (autoimmune hepatitis + primary biliary cholangitis), CTP class A (6), MELD (9). Suspected hepatocellular carcinoma (HCC) vs. nodular hyperplasia? Portal hypertension with esophageal/gastric varices, stage 4. Hypersplenism syndrome with bilinear cytopenia. Hepatocellular failure. Secondary coagulopathy. History of fetal hepatocyte transplantation (dates: 18/10/2017, 25/01/2018, 08/06/2018, 18/02/2019). History of radiofrequency ablation (RFA) of liver lesion in the 3rd segment on 10/11/2019.

Peripheral neuropathy

Complaints of numbness, reduced sensation, muscle weakness, and tremor.



CT of the brain reveals moderate subcortical and cortical atrophy, which is atypical for the patient's age.

4

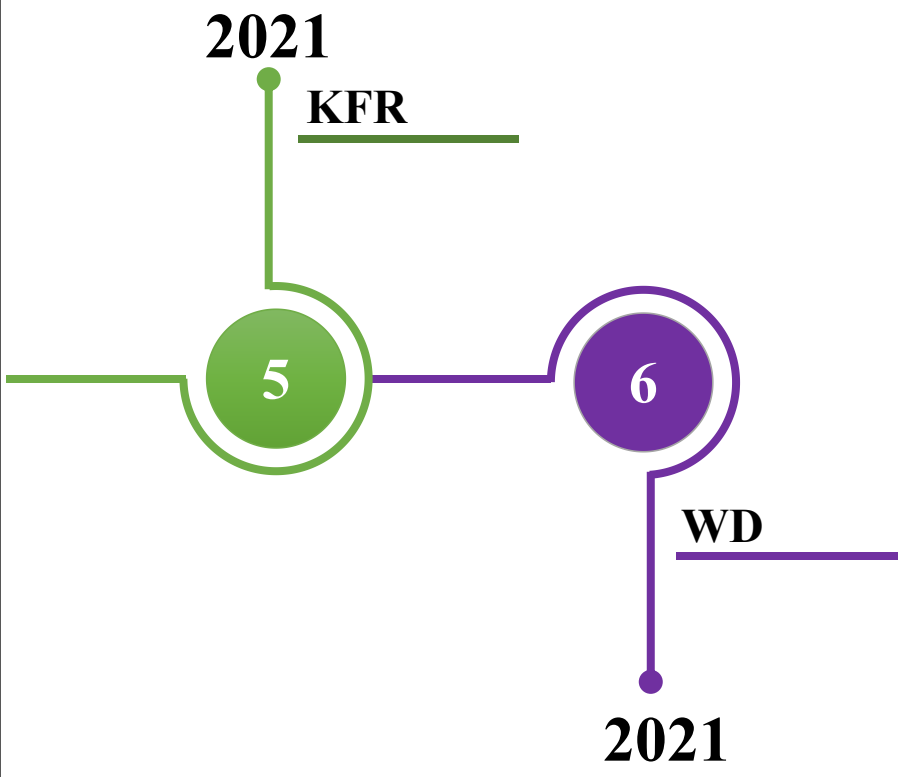
NS

2020

2021

Shuffling gait
Handwriting (jumpy, illegible)

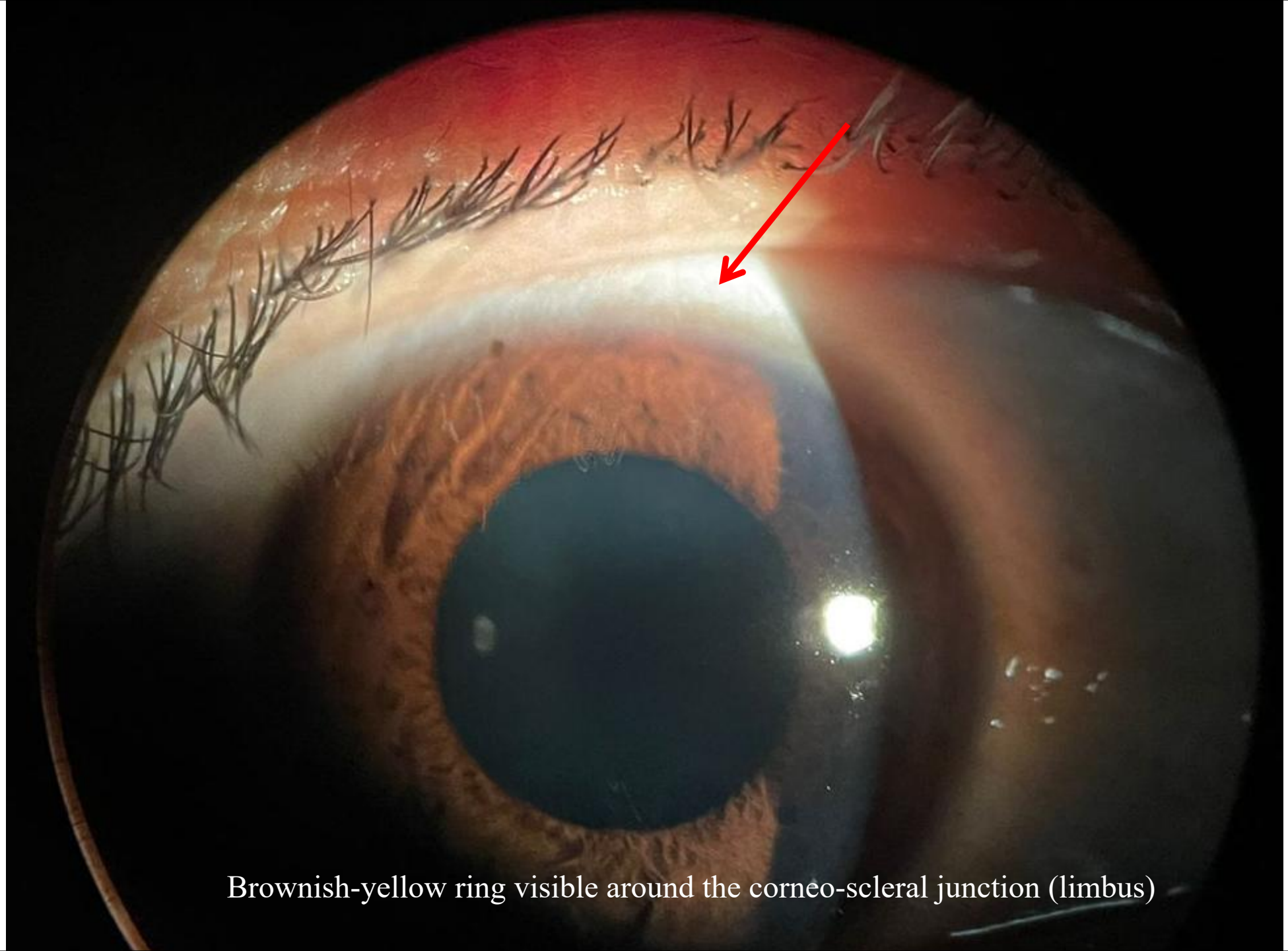
Wilson disease



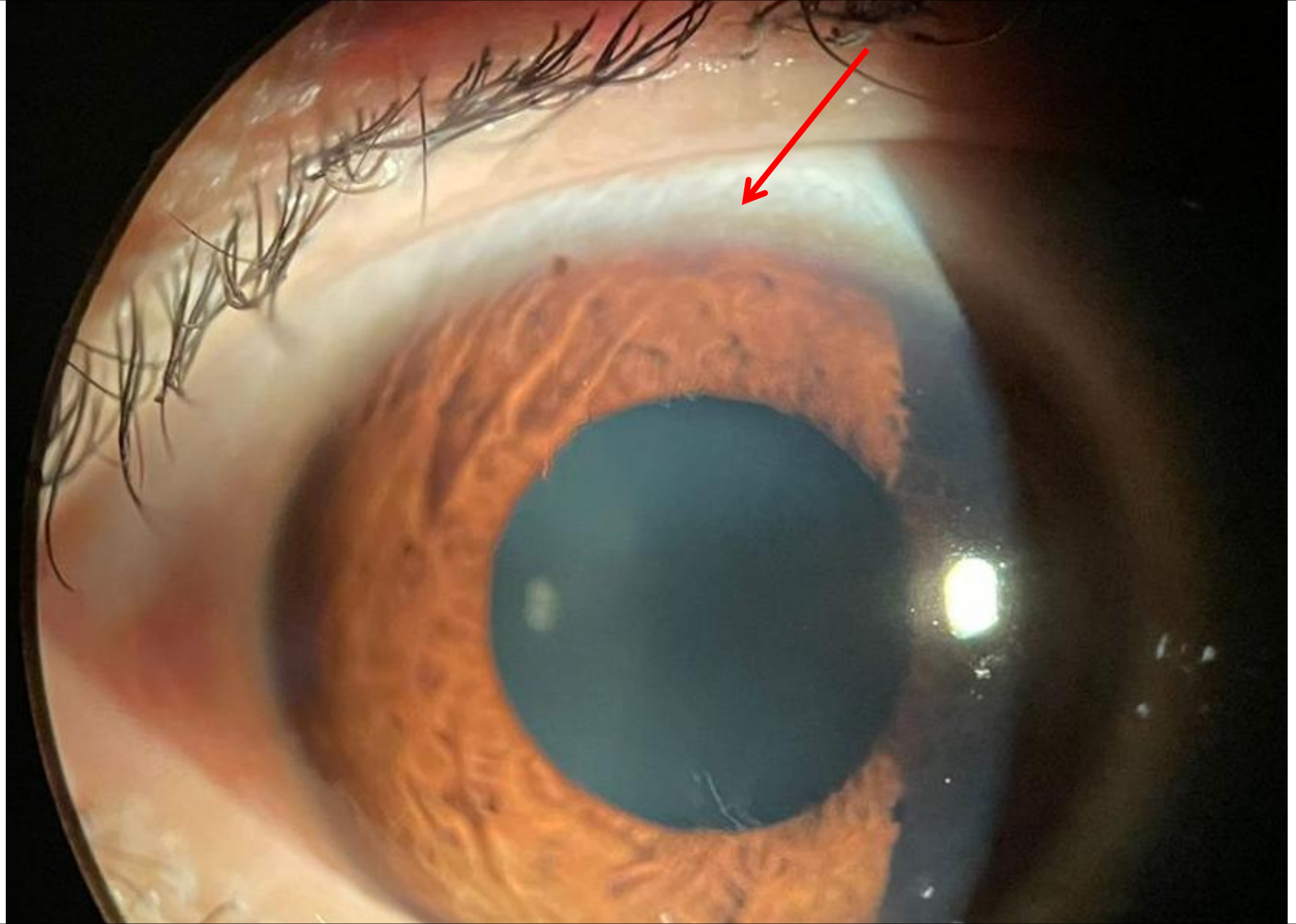
Ceruloplasmin: 0.19 mg/L (significantly below normal range of 200-600 mg/L).

24-h urinary copper excretion: 234 mcg/day (normal 3-45 mcg/day)

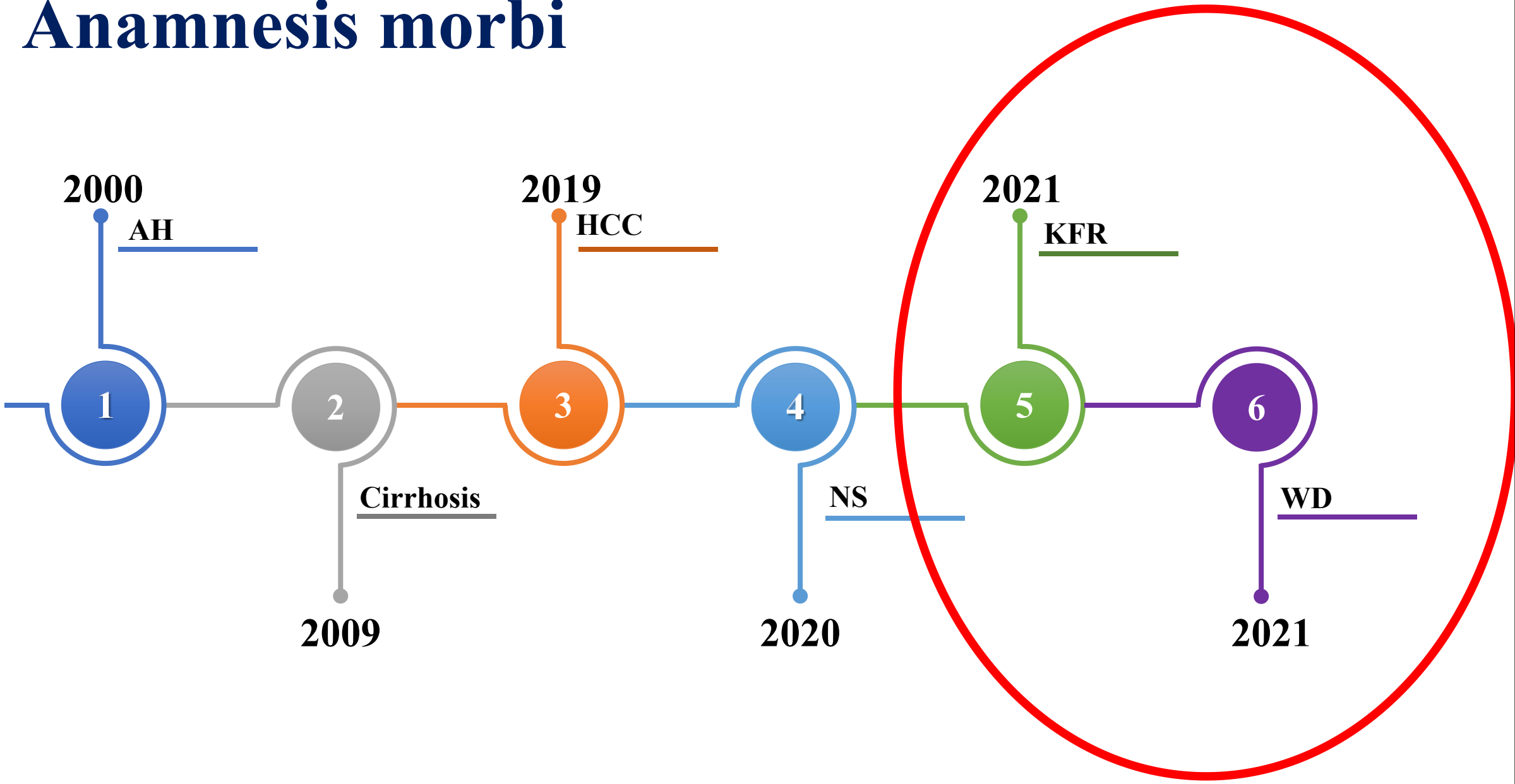
Ophthalmology consultation



Brownish-yellow ring visible around the corneo-scleral junction (limbus)



Anamnesis morbi



Leipzig score for diagnosis of Wilson disease

Parameters/Specific clinical features	Points
Kayser–Fleischer rings	
• Present	2
• Absent	0
• Neuropsychiatric symptoms suggestive	
• Present	2
• Absent	0
Coombs-negative hemolytic anemiaИмеется	
• Present	1
• Absent	0

Laboratory tests	Points
24-h urinary copper excretion (in the absence of acute hepatitis)	
• Normal	0
• 1–2× ULN	1
• >2× ULN 2	2
• Normal but >500 µg/day 1 day after challenge with 2× 500 mg d-penicillamine (see notec)	2
Liver copper quantitatived	
• Normal (ULN = 50 µg/g dry weight)	-1
• Up to 5× ULN	1
• >5× ULN	2
• Rhodanine-positive hepatocyte Present	0
• Rhodanine-positive hepatocyte Absent	1
Serum ceruloplasmin (nephelometric assay, LLN = 20 mg/dle)	
• Normal	0
• 10–20 1	1
• <10	2
Mutation analysis (ATP7B)	
• Disease-causing mutations on both chromosomes	4
• Disease-causing mutation on one chromosome	1
• No disease-causing mutation detected	0

Total score	Assessment
≥4	Diagnosis of Wilson disease highly likely
2-3	Diagnosis of Wilson disease probable, do more investigations
0-1	Diagnosis of Wilson disease unlikely

A multidisciplinary approach to the diagnosis and management of Wilson disease: Executive summary of the 2022 practice guidance on Wilson disease from the AASLD. Hepatology ():p n/a, December 07, 2022. | DOI: 10.1002/hep.32805

Leipzig score for diagnosis of Wilson disease

Parameters/Specific clinical features	Points
Kayser–Fleischer rings • Present • Absent	 2 0
• Neuropsychiatric symptoms suggestive • Present • Absent	 2 0
Coombs-negative hemolytic anemiaИмеется • Present • Absent	 1 0

Laboratory tests	Points
24-h urinary copper excretion (in the absence of acute hepatitis) • Normal • 1–2× ULN • >2× ULN 2 • Normal but >500 µg/day 1 day after challenge with 2× 500 mg d-penicillamine (see notec)	 0 1 2 2
Liver copper quantitatived • Normal (ULN = 50 µg/g dry weight) • Up to 5× ULN • >5× ULN • Rhodanine-positive hepatocyte Present • Rhodanine-positive hepatocyte Absent	 -1 1 2 0 1
Serum ceruloplasmin (nephelometric assay, LLN = 20 mg/dle) • Normal • 10–20 1 • <10	 0 1 2
Mutation analysis (ATP7B) • Disease-causing mutations on both chromosomes • Disease-causing mutation on one chromosome • No disease-causing mutation detected	 4 1 0

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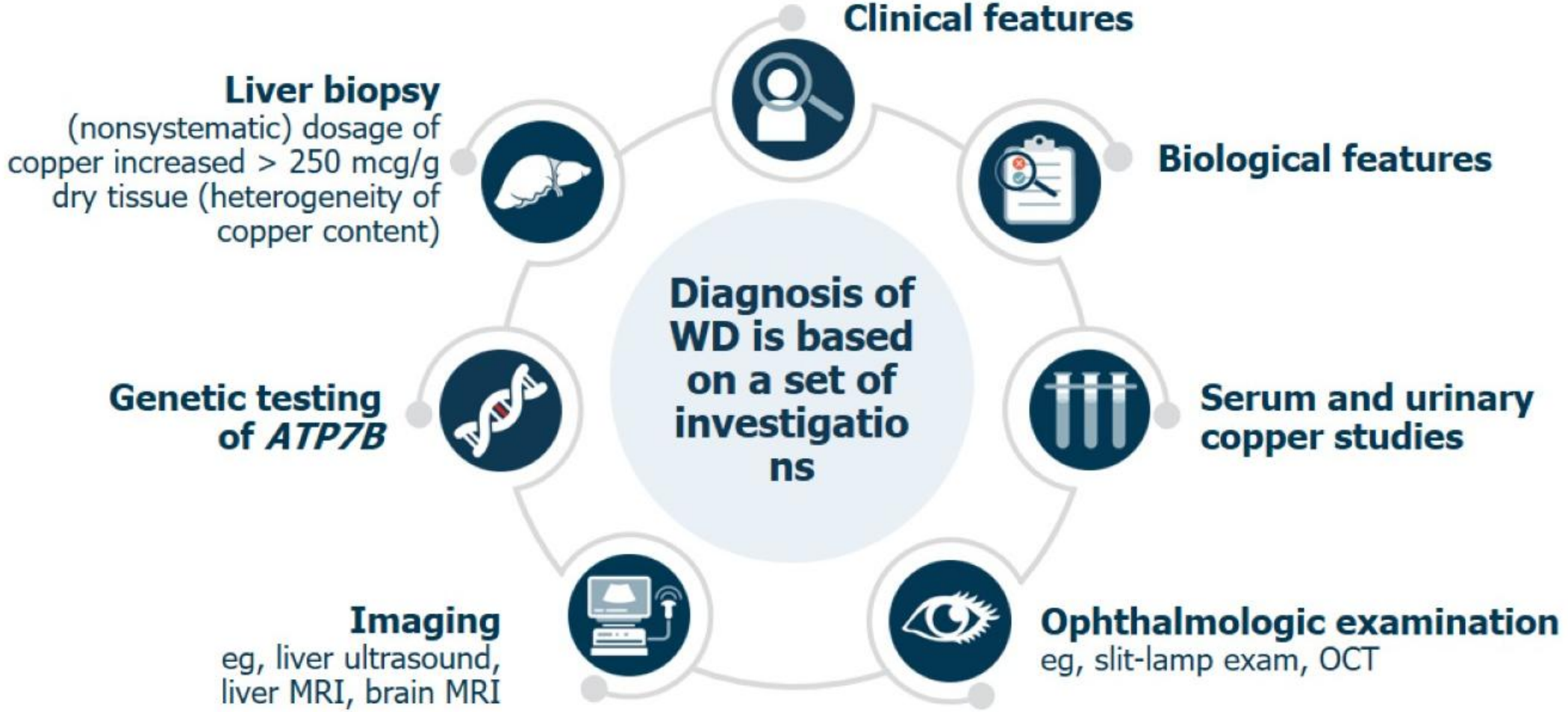
Diagnostic



OCT, optical computed tomography.

Poujois A, et al. Clin Res Hepatol Gastroenterol. 2018;42:512-520.

Lifelong therapy

Drug	Mode of action	Neurological worsening	Side effects	Comments
D-Penicillamine	General chelator induces renal excretion of copper	10%–20% during initial phase of treatment	• Fever, rash, proteinuria, lupus-like reaction • Aplastic anemia • Leukopenia • Thrombocytopenia • Nephrotic syndrome • Degenerative changes in skin • Elastosis perforans serpiginosa • Serous retinitis • Hepatotoxicity • Colitis	Reduce dose for surgery to promote wound-healing and during pregnancy
Trientine	General chelator induces renal excretion of copper	10%–15% during initial phase of treatment	• Gastritis • Aplastic anemia rare • Sideroblastic anemia • Colitis	Reduce dose for surgery to promote wound-healing and during pregnancy
Zinc	Metallothionein inducer, blocks intestinal copper absorption	Can occur during initial phase of treatment	• Gastritis • Biochemical pancreatitis • Zinc accumulation • Possible changes in immune function	No dosage reduction for surgery or pregnancy

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Treatment

	Initial therapy	Maintenance therapy
AASLD_2022	Chelators	Chelators ± Zinc
British ASL_2022	Chelator (DPA)	Chelators ± Zinc
EASL_2012	Chelators	Chelators ± Zinc
ESPGHAN_2018	Chelators ± Zinc	Zinc

- All recommendations include chelators as a 1st line of therapy
  The FDA recommends DPA as the 1st line of therapy, although there are reports of successful use of other drugs (Trientin and Zinc)

a. EASL. J Hepatol. 2012;56:671-685; b. Schilsky ML, et al. Hepatology. 2022;10.1002/hep.32805; c. Socha P, et al. J Pediatr Gastroenterol Nutr. 2018;66:334-344; d. FDA. D-penicillamine

Management

Initial

- Penicillamine or trientine chelation therapy
- Monitor for paradoxical neurological worsening
- Early referral to transplant centre if acute liver failure suspected
- Offer family screening to first-degree relatives

Lancet Gastroenterol Hepatol 2022 Published Online April 13, 2022 https://doi.org/10.1016/ S2468-1253(22)00004-8

Management

Initial

- Penicillamine or trientine chelation therapy
- Monitor for paradoxical neurological worsening
- Early referral to transplant centre if acute liver failure suspected
- Offer family screening to first-degree relatives

Long term

- Regular follow-up every 6–12 months
- Monitor copper indices and check treatment adherence
- Multidisciplinary input
- HCC surveillance in cirrhosis

Lancet Gastroenterol Hepatol 2022 Published Online April 13, 2022 https://doi.org/10.1016/ S2468-1253(22)00004-8

Conclusion

1. WD should be considered in any individual with liver abnormalities of uncertain cause. Age alone should not be the basis for eliminating a diagnosis of WD.

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1. WD should be considered in any individual with liver abnormalities of uncertain cause. Age alone should not be the basis for eliminating a diagnosis of WD.

2.WD must be excluded in any patient with unexplained liver disease associated with neurological or psychiatric disorder. Assessment by a neurologist specializing in movement disorders may be advantageous. Psychiatric evaluation is essential for any patient with WD presenting with psychiatric or neuropsychiatric features of WD.

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2.WD must be excluded in any patient with unexplained liver disease associated with neurological or psychiatric disorder. Assessment by a neurologist specializing in movement disorders may be advantageous. Psychiatric evaluation is essential for any patient with WD presenting with psychiatric or neuropsychiatric features of WD.

3. WD should be suspected in any patient presenting with ALF with nonimmune hemolytic anemia including acute intravascular hemolysis. These patients require urgent evaluation for liver transplantation.

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4. Evaluation for WD is critical in patients exhibiting recurrent self-limited nonimmune hemolysis.

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4. Evaluation for WD is critical in patients exhibiting recurrent self-limited nonimmune hemolysis.

5. At clinical presentation, WD may involve organ systems besides the liver and nervous system (such as renal, musculoskeletal, cardiac, or endocrine).

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4. Evaluation for WD is critical in patients exhibiting recurrent self-limited nonimmune hemolysis.

5. At clinical presentation, WD may involve organ systems besides the liver and nervous system (such as renal, musculoskeletal, cardiac, or endocrine).

6. First-degree relatives of patients newly diagnosed with WD must be screened for WD. Within a pedigree where there is one or more individuals with WD, any person with signs or symptoms consistent with WD, irrespective of closeness of relationship, should be evaluated for WD. Available strategies are genotype assessment of *ATP7B*and comprehensive clinical evaluation.

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6. Once WD is considered, a detailed personal and family medical history should be conducted and a physical examination focused on evidence of liver, neurological, and psychiatric disease performed. Assessment should include the following:

- **liver biochemistries;**
- **complete blood count and international normalized ratio (INR);**
- **serum ceruloplasmin and, in some patients, serum copper;**
- **basal 24-h urinary copper excretion;**
- **slit-lamp or optical tomography examination for KF rings;**
- **neurological evaluation; and molecular genetic investigation of *ATP7B* (depending on logistics).**

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Thank you for your attention!