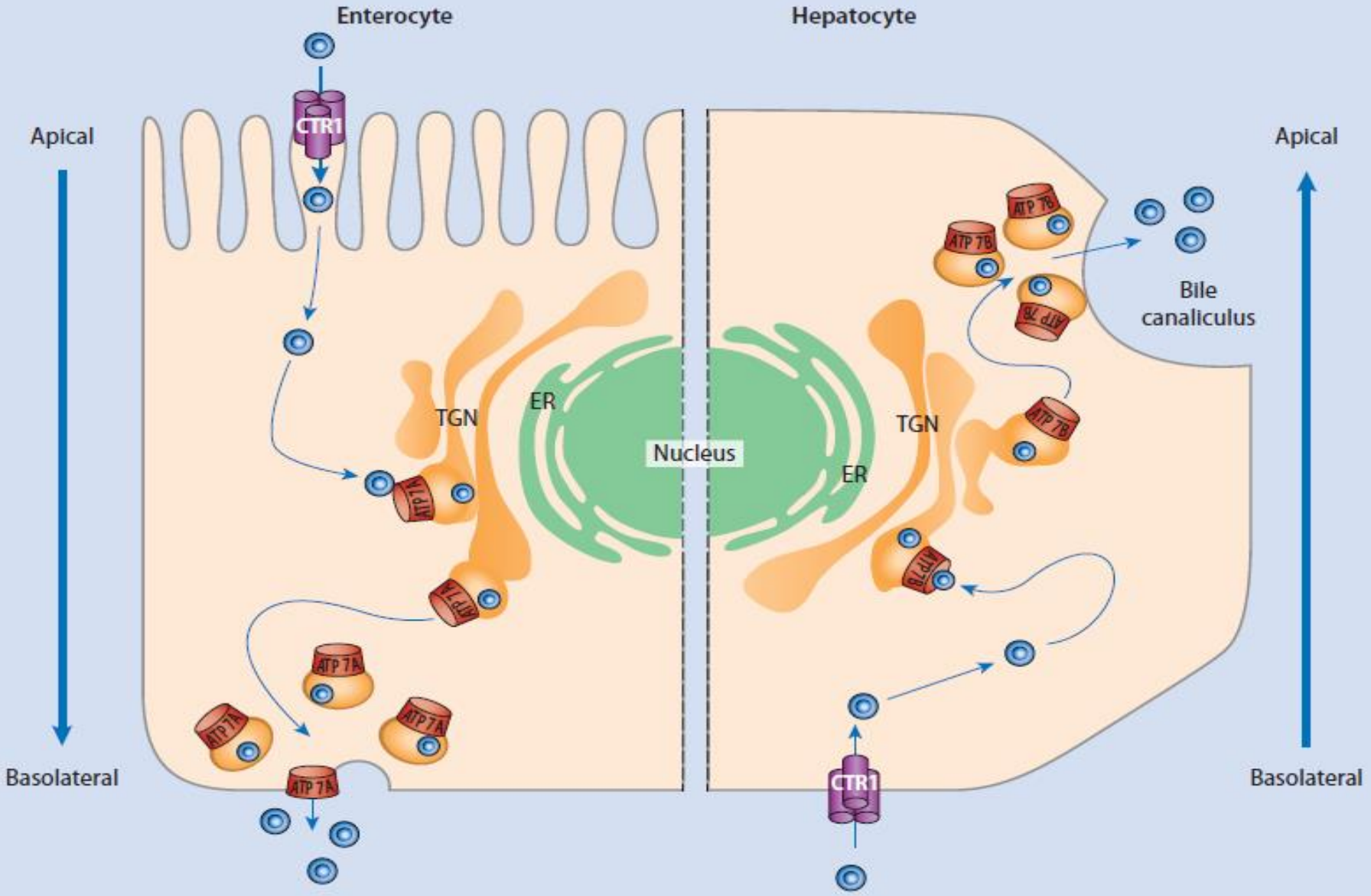
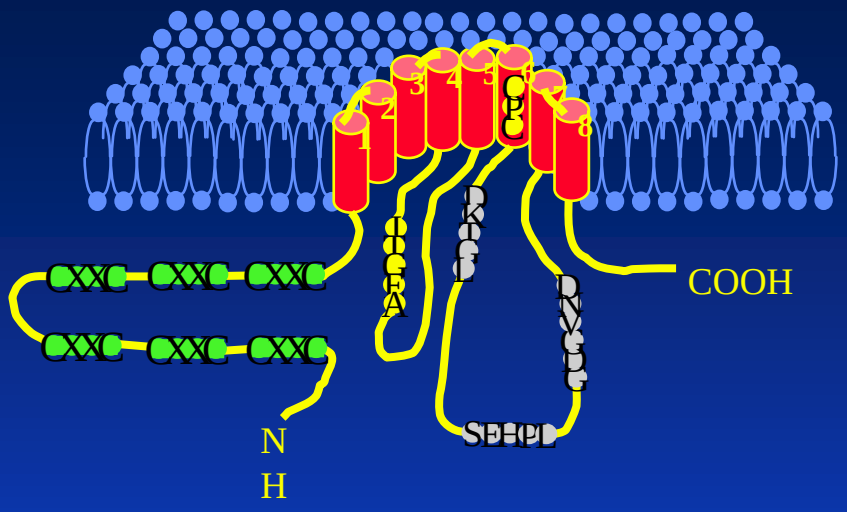
Wilson Disease

Roderick Houwen, Wilhelmina Childrens Hospital

ATP7A vs ATP7B



Wilson disease



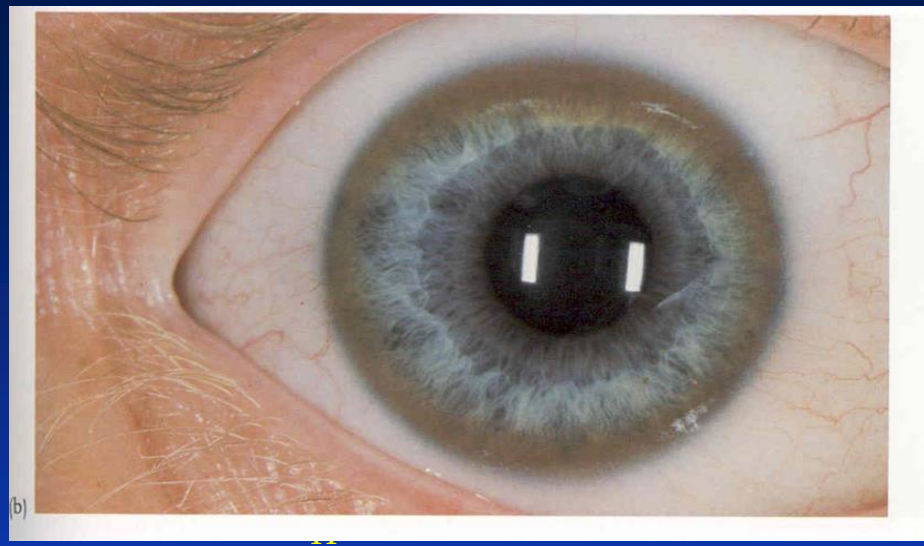
- Autosomal recessive
- Frequency 1:30.000-1:50.000
- Caused by *ATP7B* mutations

$\Rightarrow$ insufficient copper excretion by the liver

$\Rightarrow$ gradual hepatic copper accumulation

$\Rightarrow$ secundarily in brain, eyes etc

Wilson disease



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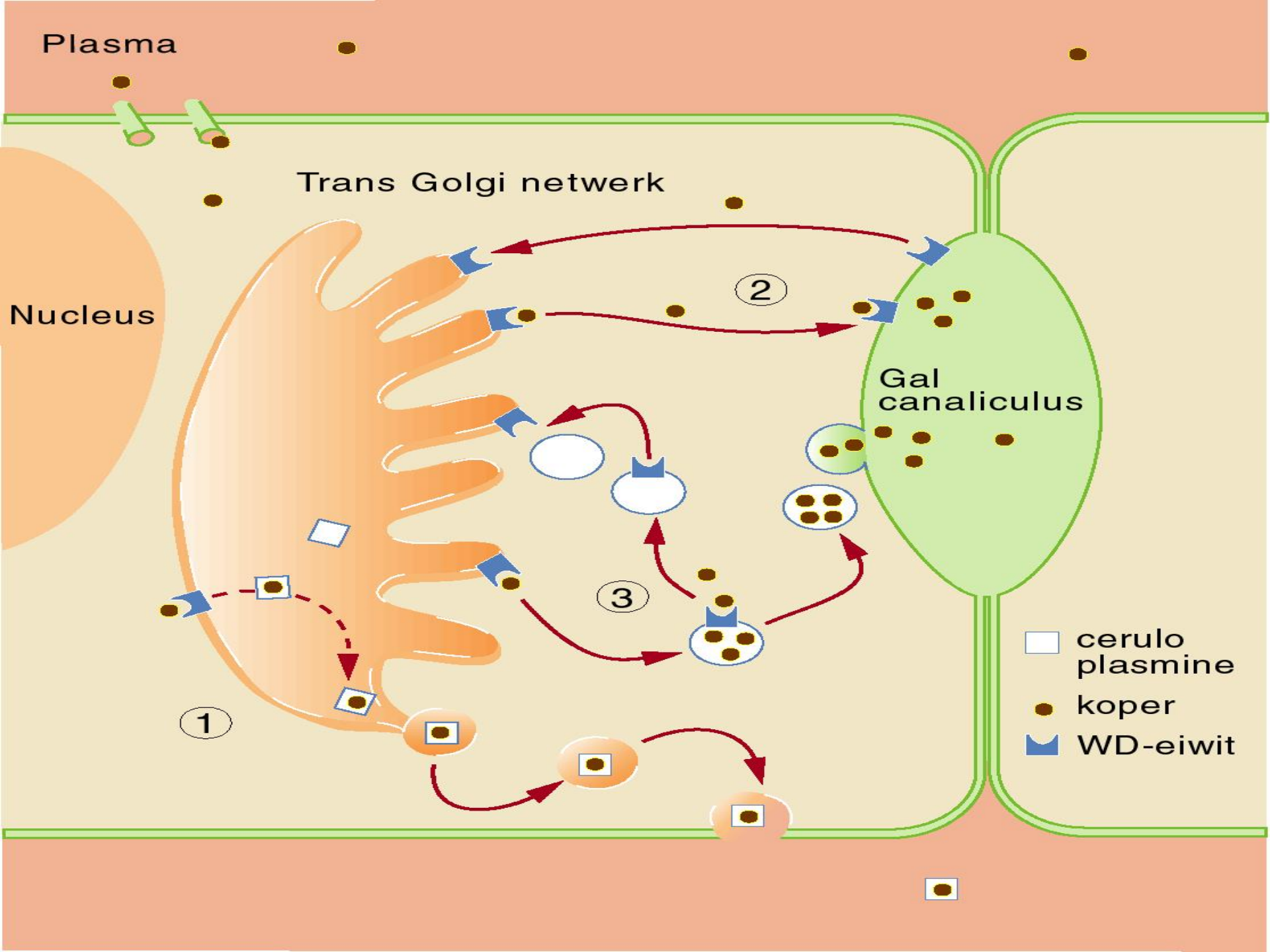

Plasma
Trans Golgi netwerk
Nucleus
2
Gal
canaliculus
3
1
cerulo
plasmine
koper
WD-eiwit

Wilson Disease: diagnostic problems

J Hepatol 2012;56:671-85

Test	Typical finding	False "negative"	False "positive"
Serum ceruloplasmin	Decreased by 50% of lower normal value	Normal levels in patients with marked hepatic inflammation Overestimation by immunologic assay Pregnancy, estrogen therapy	Low levels in: - malabsorption - aceruloplasminemia - heterozygotes
24-hour urinary copper	>1.6 µmol/24 h >0.64 µmol/24 h in children	Normal: - incorrect collection - children without liver disease	Increased: - hepatocellular necrosis - cholestasis - contamination
Serum "free" copper	>1.6 µmol/L	Normal if ceruloplasmin overestimated by immunologic assay	
Hepatic copper	>4 µmol/g dry weight	Due to regional variation - in patients with active liver disease - in patients with regenerative nodules	Cholestatic syndromes
Kayser-Fleischer rings by slit lamp examination	Present	Absent - in up to 50% of patients with hepatic Wilson's disease - in most asymptomatic siblings	Primary biliary cirrhosis

FERENCI SCORE

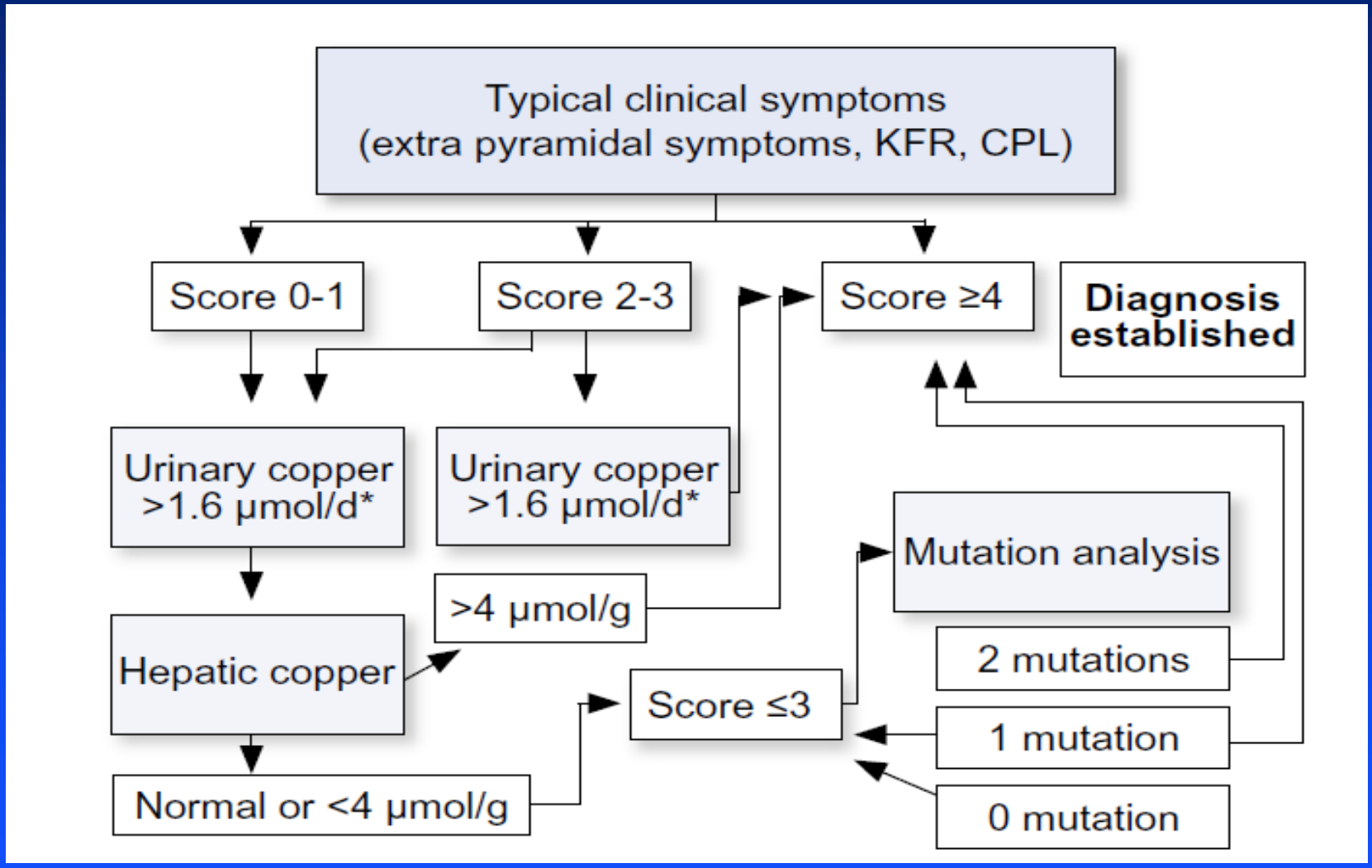
Liver Int 2003;23:139-42 and J Hepatol 2012;56:671-85

	+	-
KF ring	2	0
Neurological symptoms	2	0
Urinary copper > 1,6 µmol/d	2	0
Liver copper > 250 µg/gr	2	0
Ceruloplasmin <100 mg/l	2	0
Hemolytic anemia	1	0
One mutation	1	0
Two mutations	4	0

Diagnosis established if ≥ 4 points

DIAGNOSIS OF WILSON DISEASE

EASL guidelines, J Hepatol 2012;56:671-85



A patient with Wilson disease

- Eight years old; during holiday in Turkey icteric

- Upon return investigations by family physician:
  -Sclerae icteric, liver enlarged, spleen palpable

  -Initial laboratory: Hb 6.7 mmol/l, L 7.0x10^9/l, Thr 121x10^9/l, Bilirubin total 258µmol/l, Bilirubin conj. 158 µmol/l, ASAT 175 U/l, ALAT 115 U/l, GGT 48 U/l

A patient with Wilson disease
Childrens hospital additional investigations

- ESR 24, Hb 6,7 Thrombo 121, leuco 7,0
- Bilirubin 258/158 µmol/l
- ASAT 175 U/L, ALAT 115 U/l, GGT 48 U/l
- Albumin 24 g/l, APTT 75 sec, PT 55 sec
- Hep A -, Hep B -, Hep C -, EBV-VCA-IgM -
- Alfa-1-antitrypsin 2,2 g/l
- Immunoglobulines N, anti-SMA ±, anti-LKM -
- Ceruloplasmin: 51 mg/l (200-400)
- Copper in 24 hr urine: 27,6 µmol/l (<0.6 µmol/l)
- KF ring -, haptoglobin 1,5 g/l (0,3-2)

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Genetic confirmation: Met769fs/Q1351X

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Treatment?

A patient with Wilson disease
Treatment modalities

Chelators: quick, but side effects

-Penicillamin

-Trientine

-Tetrathiomolybdate (not available at present)

Zinc: slow, rarely side effects

Liver Tx: very quick,

but short and long term morbidity/mortality

Wilson disease: Prognostic index

Dhawan Liver Transplant 2005;11:441-5

	1	2	3	4
•Bilirubin	101-150	151-200	201-300	>301
•ASAT	101-150	151-300	301-400	>401
•INR	1.3-1.6	1.7-1.9	2.0-2.4	>2.5
•WCC	6.8-8.3	8.4-10.3	10.4-15.3	>15.4
•Albumin	34-44	25-33	21-24	<20

Score ≥ 11: Survival without LTx unlikely

Score ≤ 11: Chelator will generally suffice

Wilson disease: Prognostic index

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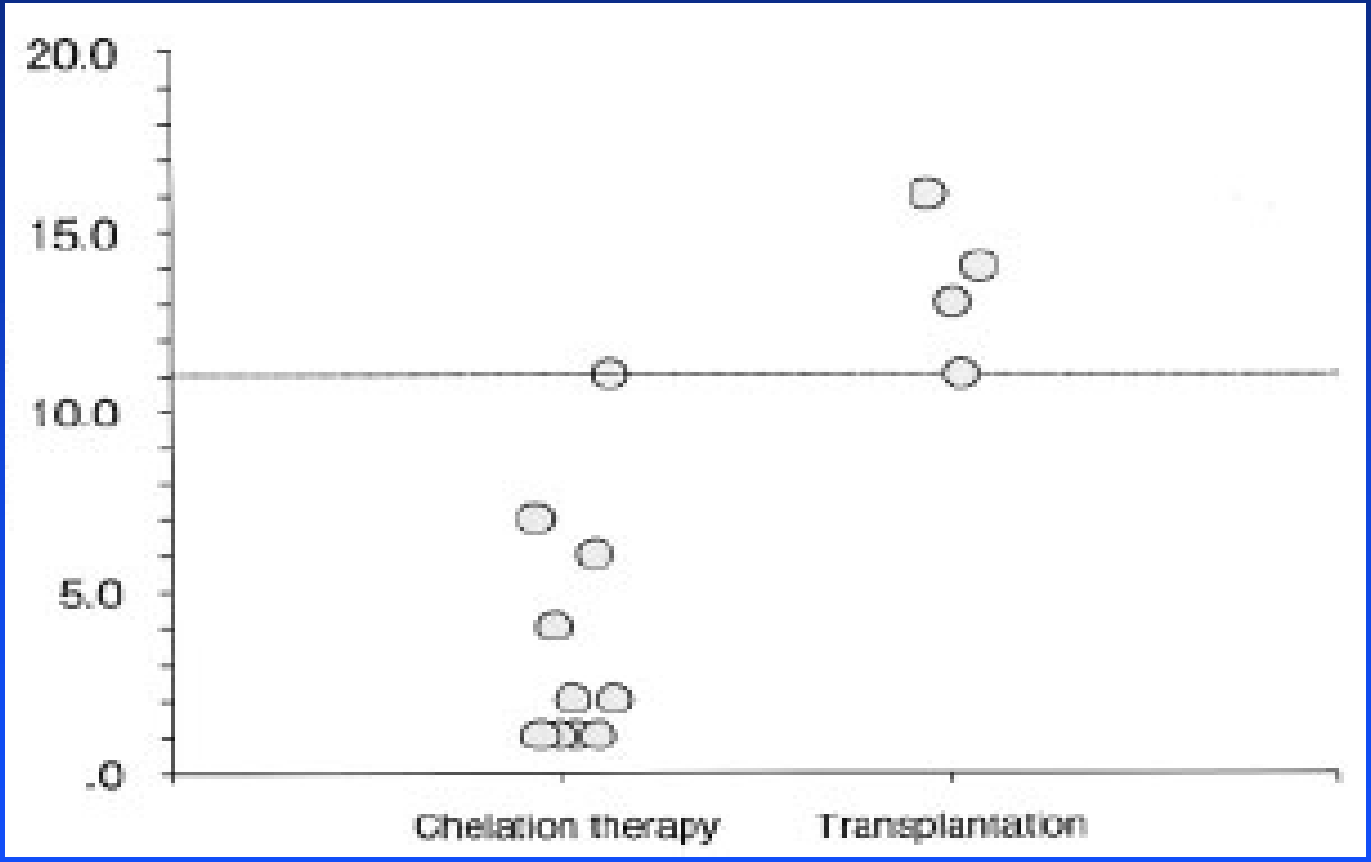

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A patient with Wilson disease

1. Liver failure
   - Listed for LTx
   - Diet: protein restricted (NH_4 normal)
   - Ascites → Rx spironolactone

2. Chelator on waiting list
   -Rx D-penicillamin 4x 250 mg

A patient with Wilson disease

1. Liver failure
   - Listed for LTx → **succesful procedure**
   - Diet: protein restricted (NH_4 normal)
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A patient with Wilson disease
Childrens hospital additional investigations

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- Copper in 24 hr urine: 27,6 μmol/l (<0.6 μmol/l)
- KF ring -, haptoglobin 1,5 g/l (0,3-2)

Liver failure with low ASAT/ALAT

A patient with Wilson disease

Nat Med 1998;4:588-93/Nat Med 2007;164-70

Hepatic failure and liver cell damage in acute Wilson's disease involve CD95 (APO-1/Fas) mediated apoptosis

- ASAT 175 U/L, ALAT 115 U/l, GGT 48 U/l
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A patient with Wilson disease

Nat Med 1998;4:588-93/Nat Med 2007;164-70

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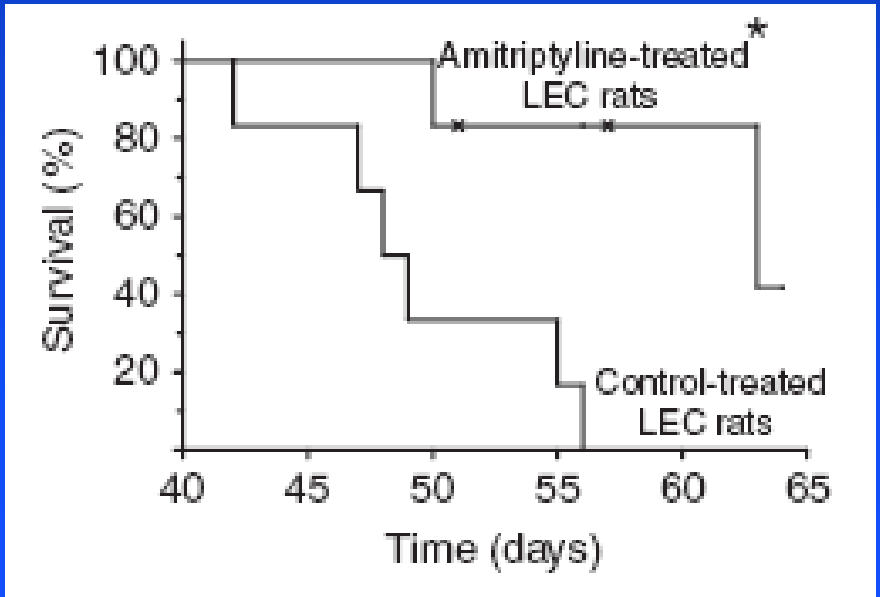

Two patients with Wilson disease

- Three sibs, one Met769fs/Q1351X
- Symptom free (“presymptomatic”)
- Lab: ASAT 74 U/l, ALAT 120 U/l, INR 1.2
  ceruloplasmin 110 mg/dl, 24 hr urine: 2,3 µmol/l

Treatment?

META-ANALYSIS: TREATMENT

Wiggelinkhuizen et al, Aliment Pharmacol Ther 2009;29:947-58

Table 2. Clinical efficacy of (a) D-penicillamine and (b) zinc (zinc acetate, zinc sulphate)

Initial presentation	No. studies	Patients, *n* (total sample size)*	Clinical outcome, no. patients (%)						
			Presymptomatic/ asymptomatic	Improved	Favourable outcome†	Unchanged	Deteriorated	Dead	Unfavourable outcome‡
(a)									
Presymptomatic	6	70 (85)	70 (100)		70 (100)		0 (0)	0 (0)	0 (0)
Hepatic symptoms	5	57 (86)	12 (21.1)	30 (52.6)	42 (73.7)	1 (1.8)	9 (15.8)	5 (8.8)	15 (26.3)
of which AHF	2	13	0 (0)	10 (76.9)	10 (76.9)	0 (0)	1§ (7.7)	2 (15.4)	3 (23.1)
Neurological symptoms	6	72 (111)	13 (18.1)	45 (62.5)	58 (80.6)	2 (2.8)	10 (1.4)	2 (2.8)	14 (19.4)
All presentations	9	199 (282)	95 (47.7)	75 (37.7)	170 (85.4)	3 (1.5)	19 (9.5)	7 (3.5)	29 (14.6)
(b)									
Presymptomatic	5	66 (88)	66 (100)		66 (100)		0 (0)	0 (0)	0 (100)
Hepatic symptoms	2	9 (37)	0 (0)	5 (55.6)	5 (55.6)	1 (11.1)	2 (22.2)	1 (11.1)	4 (44.4)
Neurological symptoms	2	10 (127)	2 (20.0)	7 (70.0)	9 (90.0)	0 (0)	1 (10.0)	0 (0)	1 (10.0)
All presentations	6	85 (252)	68 (80)	12 (14.1)	80 (94.1)	1 (1.2)	3 (3.5)	1 (1.2)	5 (5.9)

META-ANALYSIS: TREATMENT

Wiggelinkhuizen et al, Aliment Pharmacol Ther 2009;29:947-58

Severe (medication switch):

Penicillamin	26/205 (12.7%)
Zinc	2/224 (0.9%)

All side effects:

Penicillamin	50/205 (24.4%)
Zinc	28/224 (12.5%)

PRESYMPTOMATIC PATIENTS
Treatment?

EASL guidelines, J Hepatol 2012;56:671-85

Treatment of presymptomatic patients or those with neurological disease on maintenance therapy can be accomplished with a chelating agent or with zinc
GRADE II-1, B, 1
AASLD Class I, Level B

If zinc is used, careful monitoring of transaminases is needed, with changing to chelators if these laboratory parameters are increasing
GRADE C1
AASLD Class I, Level B

Two patients with Wilson disease

- Three sibs, one presymptomatic
- Lab: ASAT 74 U/l, ALAT 120 U/l, INR 1.2
  ceruloplasmin 110 mg/dl, 24 hr urine: 2.3 µmol

Rx: Wilzin 3dd 25 mg

- At 3 yr: ASAT 28 U/l, ALAT 19 U/l,
  24 hr urinary copper 0.65 µmol

Another patient with Wilson disease

- Father Wilson disease: c.3687insCA/H1069Q
- Mother carrier: P1379S
- Newborn son: c.3687insCA/P1379S

What to do?

- Treat immediately ?
- Treat at 2 years of age ?
- Await laboratory signs of copper overload ?

Another patient with Wilson disease
Consequences of extreme decoppering

- Leucopenia/neutropenia
- Myelopathy and/or myopathy

Patient no	Serum ceruloplasmin (mg/dl) normal range 25–45	Total serum copper (μg/dl) normal range 70–140	Urinary copper excretion (μg/24 h) normal range 0–50	WBC (K/μl) normal range 4.5–10.5	Neutrophils ($\times 10^9$/L), normal range 2.0–7.5	RBC (M/μl) normal range 4.10–5.10	HGB (g/dl) normal range 12–15.5
Patient 1							
WD diagnosis (1996)	9.25	35	135	5.9	3.8	4.5	13.7
Overtreatment (2012)	**0.92**	**<5**	**11**	2.9	2.1	4.7	13.5
Follow-up after 6 months (2013)	5	20	12.5	6.0	4.1	4.5	12.9
Patient 2							
WD diagnosis (2008)	7.7	105	394	5.2	3.5	4.1	12.2
Overtreatment (2012)	**0.5**	**<5**	**6**	1.86	0.89	4.0	12.0
Follow-up after 12 months (2013)	1.18	5	10.5	3.3	2.0	4.2	12.5
Patient 3							
WD diagnosis (2007)	14	44	15	4.7	3.0	4.9	14.5
Overtreatment (2012)	**0.9**	**7**	**12**	2.3	0.17	3.2	10.0
Follow-up after	17	44	10	7.3	5.1	5.0	14.7

Another patient with Wilson disease

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What to do?

- ASAT, ALAT, urinary copper excretion 2x/year
- Age 10 yr: ASAT 25 U/l, ALAT 12 U/l,
  urinary copper 0.4µmol/24 hrs

Genetic vs symptomatic Wilson disease

A genetic study of Wilson's disease in the United Kingdom

"…the frequency of pathogenic mutations was 0.056…"

Genetic vs symptomatic Wilson disease

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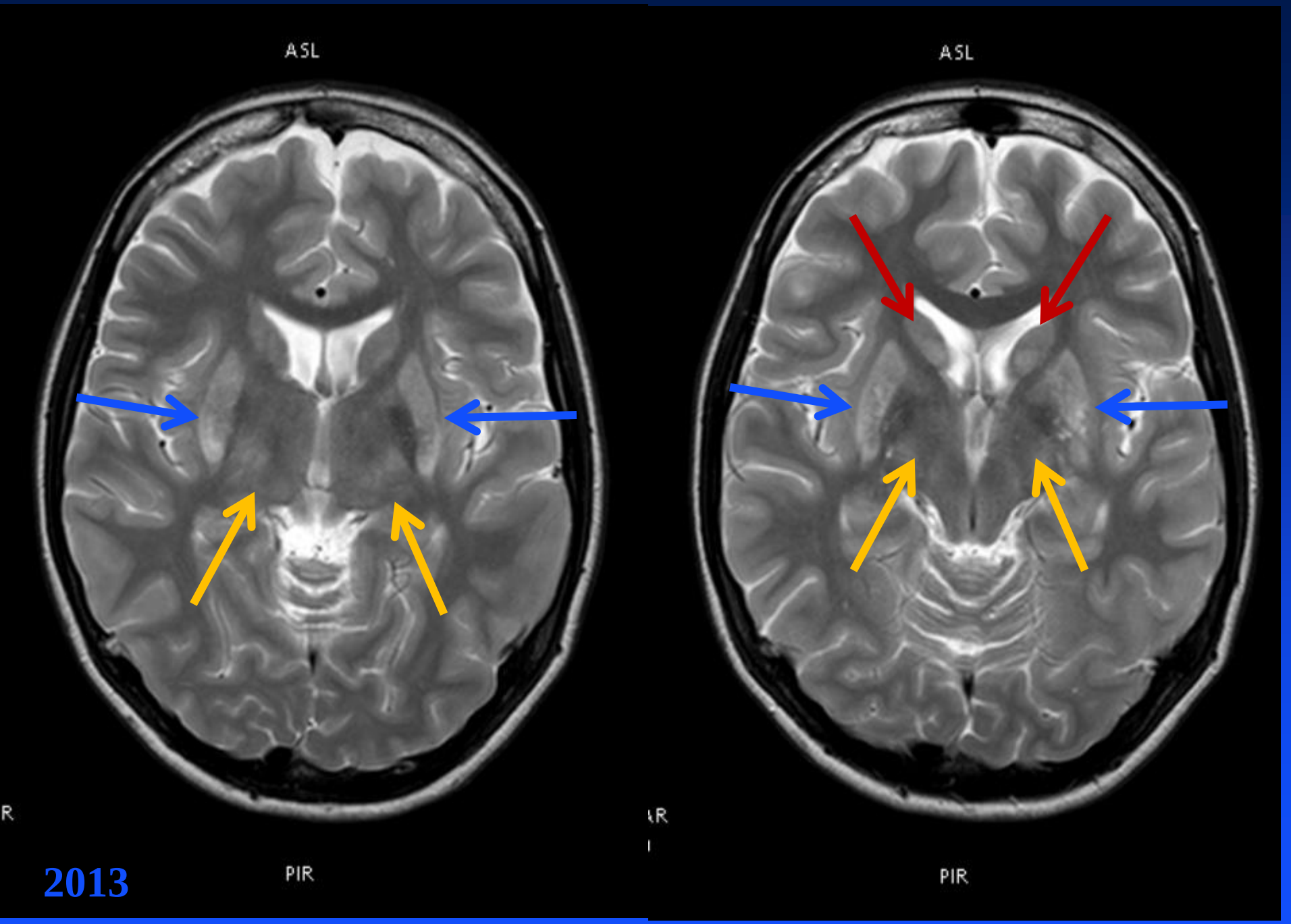
Wilson Disease in Septuagenarian Siblings: Raising the Bar for Diagnosis

Female patient with classical Wilson disease

Brother with minimal neurological disease + KF rings

A patient with neurological symptoms

- Girl, 16 years old
- Deteriorating handwriting; swallowing problems
- KF ring, 24 hr urine 3.1 µmol/24 hr, CP 120 mg/l
- ATP7B: H1069Q/H1069Q
- ASAT 47 U/L, ALAT 22 U/L, GGT 77 U/L
- Sonography: liver and spleen normal
- MRI


ASL
PIR
2013
ASL
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What to do?

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META-ANALYSIS: SIDE EFFECTS

Wiggelinkhuizen et al, Aliment Pharmacol Ther 2009;29:947-58

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D-penicillamine vs zinc

Czlonkowska et al, Eur J Neurol 2014;21:599-606

	Neurological WD		
	DPA (n = 35) (%)	ZS (n = 21) (%)	P
Early worsening (within 180 days)	12 (35.3)[a]	4 (19.0)	0.236
Change from first-line therapy			
Any time during follow-up	7 (20.0)	5 (23.8)	0.748
Within 180 days from initiation	4 (11.4)	0 (0.0)	0.286
Outcome at the end of follow-up			
Therapeutic success	29 (82.8)	15 (71.4)	0.334
Death	4 (11.8)	1 (4.8)	0.639
Lost independence	1 (2.9)	1 (4.8)	1.000

A patient with neurological symptoms

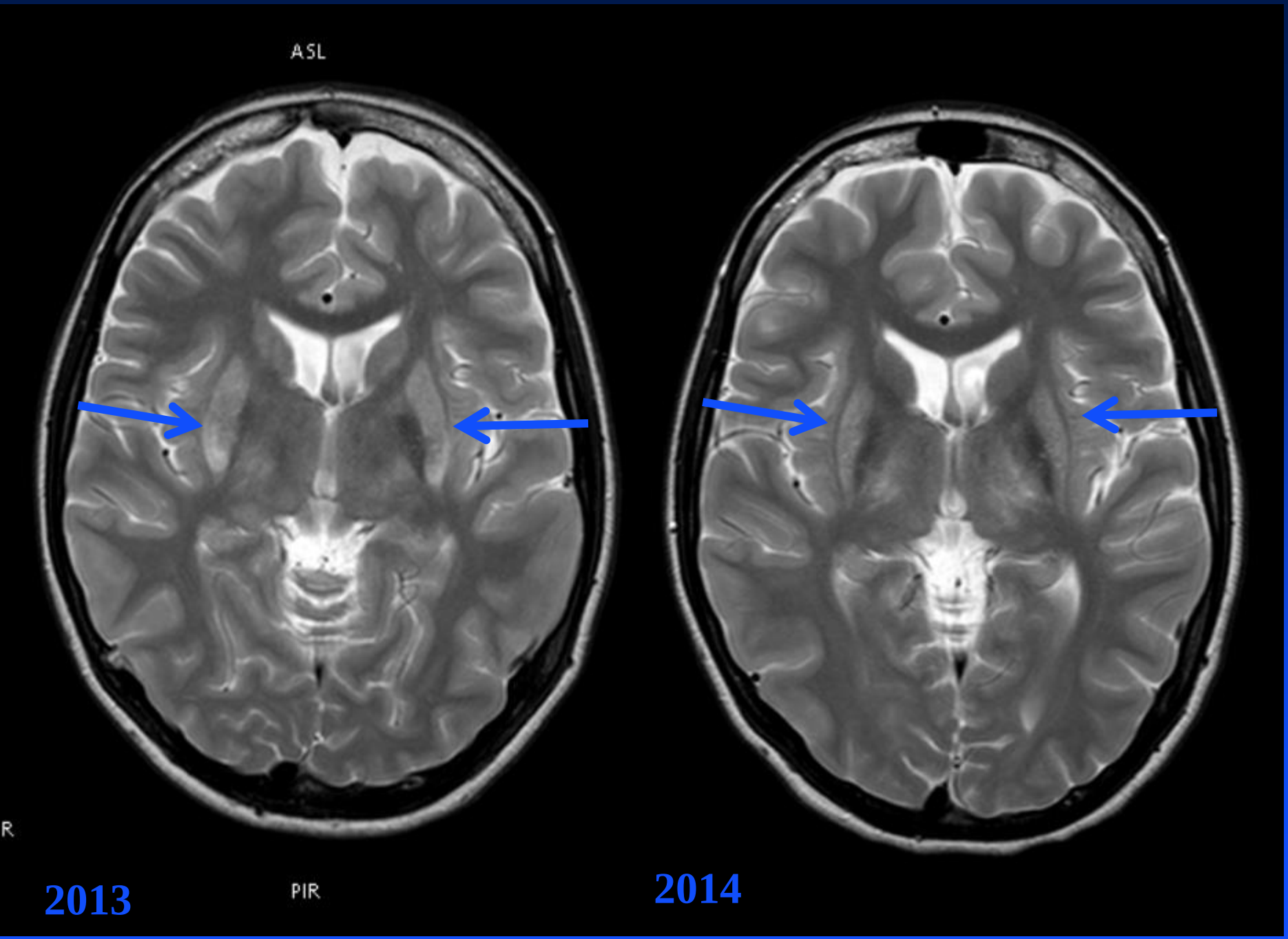
EASL guidelines (2012)

Initial treatment for symptomatic patients with Wilson's disease should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated
GRADE II-1, B, 1
AASLD Class I, Level B

Zinc may have a role as a first line therapy in neurological patients
GRADE II-2, C, 2
AASLD Class II, Level C

What we did: Wilzin 3dd 50 mg

→ slow recovery of neurological symptoms



2013

2014

Wilson Disease: current challenges

- Medical treatment of liver failure
  -apoptosis inhibitors and/or tetrathiomolybdate?
- (Initial) treatment of neurological disease
  -zinc or chelator (followed by zinc)?
  -initial role of TTM?
- Treatment of “presymptomatic” patients?
  -zinc or chelator?
- When to treat genetic Wilson disease?

MEERKEUZE VRAAG 1

Voor de diagnose Wilson is tenminste noodzakelijk:

1. verlaagd serum ceruloplasmine (< 100 mg/dl)
2. ring van Kayser Fleischer aanwezig
3. verhoogde koper uitscheiding in urine (>1,6 µmol/24 uur)
4. twee van deze parameters

MEERKEUZE VRAAG 2

Patient AB is de broer van een 21 jarige vrouw bij wie recent de ziekte van Wilson is vastgesteld. Hij heeft geen symptomen, behoudens een iets verhoogde koper uitscheiding in de urine (2.2 µmol/24 uur) en een ASAT en ALAT net boven normaal (resp 51 en 43 U/L). Analyse van het ATP7B gen laat dezelfde mutaties zien als bij zijn zus. Welke behandeling stelt u in?

-zink

-penicillamine

-trientine

-een chelator of zink, beiden zijn mogelijk

D-penicillamine vs zinc

Weiss et al, Gastroenterology 2011;21:1189-1198