Wilson's Disease

A 20 year old woman's 15 year journey

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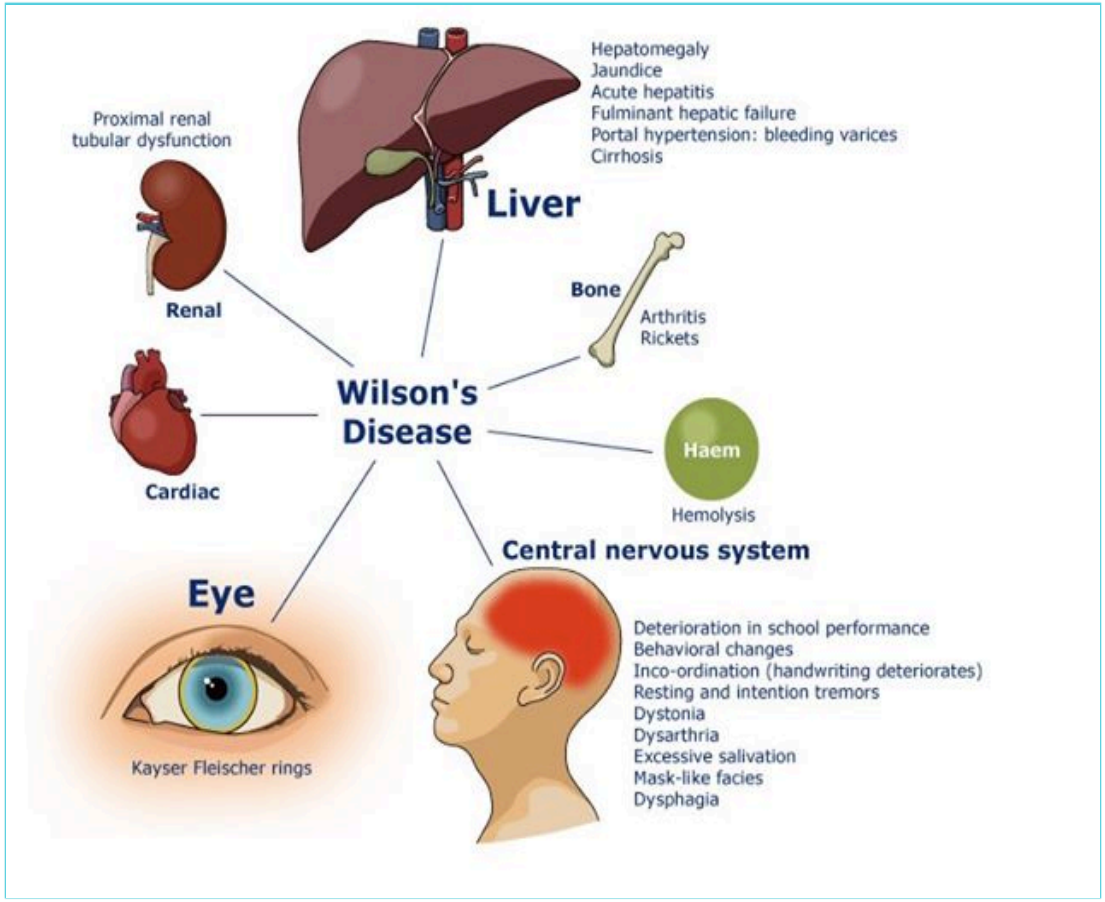
Wilson's Disease

- **Inherited disorder of copper metabolism caused by mutations of the gene ATP7B located on Chromosome 13**
  - Encodes a copper-transporting P-type ATPase
  - Transports Cu from intracellular chaperone proteins into secretory pathway for biliary excretion and incorporation into apo-caeroplasmin
- Autosomal recessive mode of inheritance
- **Molecular - genetic diagnosis:** Difficult because of >500 distinct mutations and ***380 mutations involved in pathogenesis***
  - Expensive and not required for diagnosis
- Normal dietary consumption & absorption of copper exceed the metabolic need, and homeostasis of this element is maintained exclusively by the biliary excretion of copper
- **Defective biliary excretion of copper leads to its accumulation**
  - Liver and brain
  - Other extra-hepatic sites

Gastro 2003;125:1868; Hepatol 2003;37:1241; J Membr Biol 2003;191:1

Wilson's Disease: Spectrum of Disease

- **Gene frequency:** 1 in 90-150
- **Incidence:** 1 in 30 000 (based on adults presenting with neurological symptoms)
- **Age of onset:** Can present at any age, mainly between 5-35 years;
  3% present beyond 4th decade, either with hepatic or neurologic disease



Nat Clin Pract Neurology 2006;2(9): 482; AASLD Guidelines, Hepatol 2008;47(6):2089; EASL Guidelines J Hepatol 2012;56(3):671

Wilson's Disease: Liver Disease

- Clinically evident liver disease can precede neurological manifestations by 10 years
- Most patients with neurological symptoms have some degree of liver disease at presentation

Liver disease presentations

- Asymptomatic with abnormal biochemistry
- Acute liver failure (6-12% ALF cases) - 95% mortality
  - Young females: Female to male ratio is 4:1
  - Severe Coombs-negative haemolysis
  - Acute renal failure
  - Can be initial presentation or occur after stopping therapy
- Chronic hepatitis and cirrhosis
  - Clinically indistinguishable from other forms of chronic hepatitis
  - Low grade haemolysis

Lancet 1986;12:845; World J Gastro 2007;13:1711;
Eur J Pediatr 1987;146:261

Wilson Disease: Diagnosis

Often very difficult

- Great mimicker… Dependent on maintaining a high index of suspicion
  - Autoimmune hepatitis, NASH – biochemically, autoantibodies and histologically
- No single diagnostic test
- ***Slit lamp examination: Kayser-Fleischer rings***

Biochemical

- Low serum caeruloplasmin (acute phase reactant)
- Low total serum copper
- Increased 24hr urinary copper excretion (collection in non-metal container)
- **Liver biopsy remains the gold standard:** abnormally high dry hepatic copper content (80%)

Combination of KF rings and low caeruloplasmin <0.1g/L: WD

Wilson's Disease: Diagnosis

BIOCHEMISTRY		
	Normal	**Wilson's Disease**
• **Total Serum Copper (ug/dl)**	80-140	<80
• **Urine Copper (umol/24 hrs)**	0.2-0.8	>1.6
• **Serum Caeruloplasmin (g/L)**	>0.2	<0.1
• **Hepatic Copper (ug/gram dry weight)**	15-40	250-3000

Serum Free-Copper Concentration = Total Cu - Caeruloplasmin x 3.15

- Free Copper usually <100 ug/L
- **Wilson's disease : Free Copper >200 ug/L**
- **Monitoring therapy**

AASLD Guidelines: Hepatol 2008;47(6):2089; EASL Guidelines: J Hepatol 2012;56(3):671

Wilsons Disease: Diagnosis

LIVER DISEASES	HEPATIC COPPER LEVELS (ug/gram dry weight)
• **Normal**	**30**
• **Wilson's Disease**	**730**
• Primary Biliary Cholangitis	410
• Primary Sclerosing Cholangitis	245
• Extrahepatic Obstruction	130
• Alcoholic/Cryptogenic cirrhosis	40

Limitations of dry Cu weight

- Inhomogenous distribution of Cu in liver in later stages of Wilson's disease
- 1 cm core: Sampling errors: Varies from nodule to nodule

Orcein or Rhodamine stains

- Detects only lysosomal Cu deposits: reveals focal Cu stores <10% patients

AASLD Guidelines: Hepatol 2008;47(6):2089; EASL Guidelines: J Hepatol 2012;56(3):671

Wilsons Disease: Diagnosis

Other tests

- ***Coomb's negative haemolysis***: Presenting feature in 12% cases
  - Single acute case, recurrent or chronic and low grade
- ***Acute Liver Failure***
  - Alkaline Phosphatase levels <40 IU/L
  - Alkaline Phosphatase elevation/Total bilirubin elevation: <4
  - Increased AST/ALT ratio >2:2
- ***D-Penicillamine challenge test in children:*** 24hr Urinary Cu excretion
  - 500mg D-Penicillamine administered at beginning and 12 hours later
  - **Positive test: >25umol/24hours**
  - **Unreliable to exclude diagnosis in asymptomatic siblings**
  - Not recommended in adults

Hepatology 1992;15:609; Aliment Pharmacol Ther 2004;19:157

Scoring system: 8th International Meeting on Wilson's disease, Leipzig 2001

Typical clinical symptoms and signs	
KF rings	
Present	2
Absent	0
Neurologic symptoms**	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>0.2 g/L)	0
0.1-0.2 g/L	1
<0.1 g/L	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

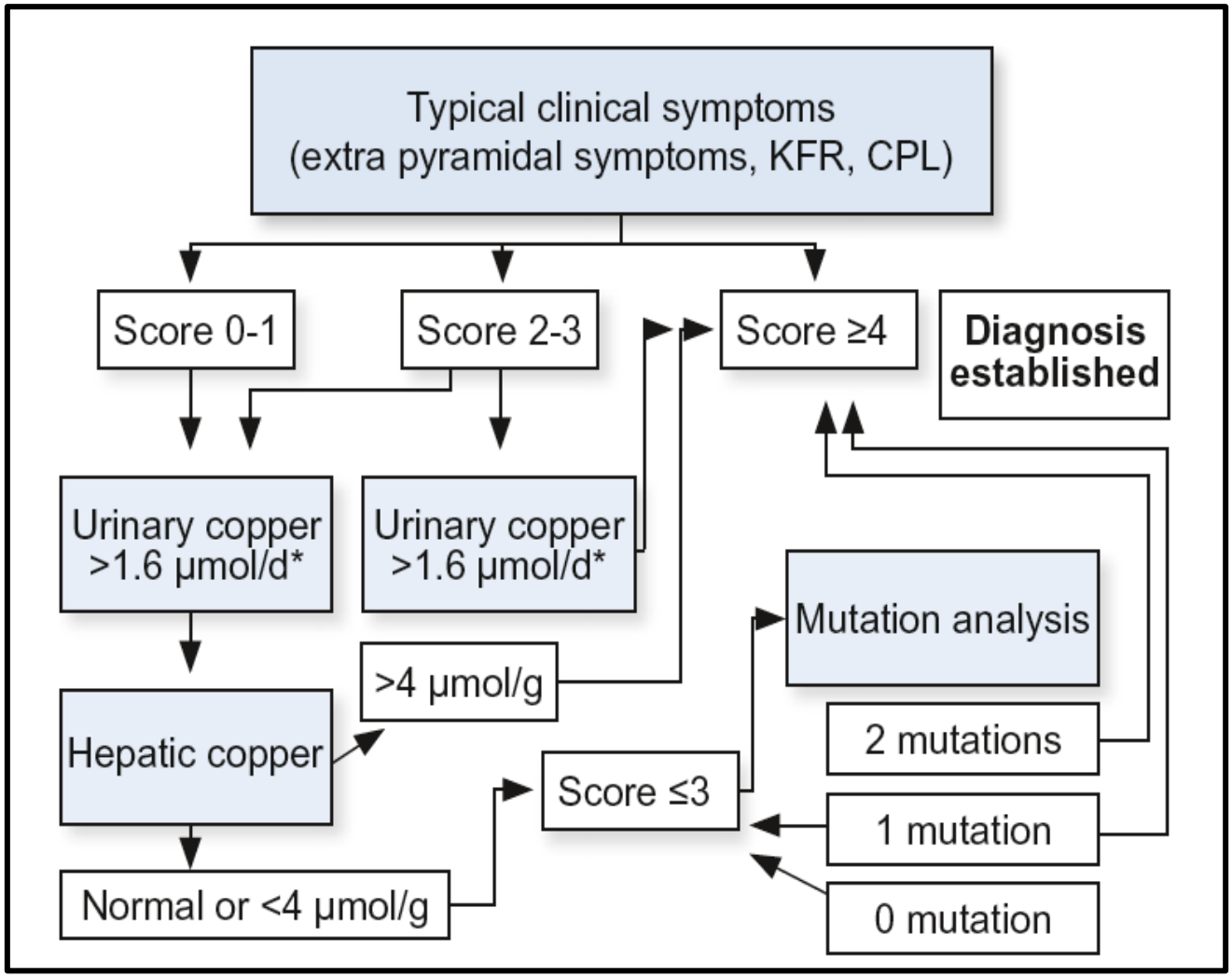
Other tests	
Liver copper (in the absence of cholestasis)	
>5x ULN (>4 μmol/g)	2
0.8-4 μmol/g	1
Normal (<0.8 μmol/g)	-1
Rhodanine-positive granules*	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1-2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	0

TOTAL SCORE	Evaluation:
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

*If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging. KF, Kayser–Fleischer; ULN, upper limit of normal.

Liver International 2003;23:139; Hepatology;52:1948

Diagnostic Algorithm: Leipzig score



Liver Int 2003:23:139

Wilson's Disease: Prognosis

- Universally fatal, if untreated
- Majority die from complications of liver disease
- Minority die from progressive neurologic disease: Debilitating disease
- Chelation therapy and liver transplantation has changed prognosis
- Liver function improves after 1-2 years of chelation therapy
  - Compliance essential

	1*	2*	3*	4*
Serum bilirubin (μmol/L)	100-150	151-200	201-300	>300
AST (U/L)	100-150	151-300	301-400	>400
INR	1.3-1.6	1.7-1.9	2.0-2.4	>2.4
WBC [10^9/L]	6.8-8.3	8.4-10.3	10.4-15.3	>15.3
Albumin [g/L]	34-44	25-33	21-24	<21

King's College Prognostic score: ≥11, high probability of death without Liver Tx

Gut 1986;27:1377; Liver Transplant 2005;11:441

Case Vignette

35 year old mother of 2 girls

- **2000:** 1st presented to GSH at age 20 with decompensated liver disease following a variceal bleed
  - Encephalopathic, coagulopathy & tense ascites
- **Wilson's Disease**
  - 3 x elevated 24hr urinary copper levels: 8, 7.6 and 9.2 umol/24hr
  - Kayser-Fleischer rings
- Commenced on Penicillamine in gradually increasing doses
- Assessed for Liver transplantation but deferred as had an excellent response to Penicillamine
  - Regained good synthetic function
  - Ascites resolved
  - No further GIT bleeds

Treatment History

- Remained on D-penicillamine until her 2 pregnancies between 2003 & 2005 – STOPPED treatment of her own accord
- Recommenced D-penicillamine in 2005 & continued until 2010
- Changed to Zinc in 2010 as D-penicillamine became unavailable in SA
- Difficulty tolerating various zinc preparations
- At the time of re-admission to the Liver Unit in 2012
  - Taking 40mg elemental zinc (optimal dose 150mg elemental zinc/day)

Clinical Course

- In 2012 referred back to the Liver unit: Re-assessment for transplantation
- **18 month history of neuropsychiatric symptoms**
  - Emotional lability
  - Dysarthria, slowed speech
  - Poor memory
  - Gait instability
  - Tremor of left hand
- Rx for Depression - Fluoxetine
- No further variceal bleeds, ascites well controlled on low dose diuretics

Family history

- Brother: Wilson's Disease diagnosed in 2006 at RXH
- Maternal cousin with neurological Wilson's Disease – bedbound, remarkable response to Trientine from a US sponsorship programme

Clinical Findings: 2012

General

- No jaundice and no peripheral stigmata of chronic liver disease
- No flap or foetor

Abdomen

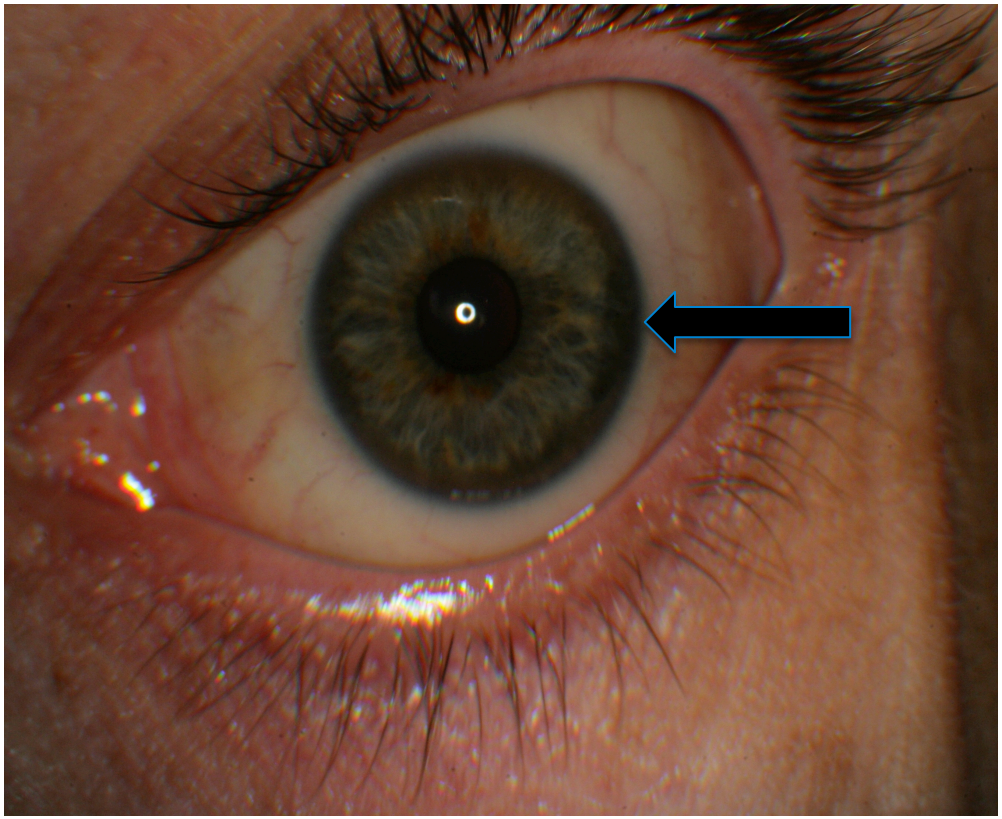
- No ascites, liver span 9 cm and 5 cm splenomegaly

Respiratory and CVS: NAD

CNS

- Emotionally labile
- Kayser-Fleischer rings
- Dysarthria, slowed speech
- Globally increased tone with cogwheeling, coarse tremor of left hand
- Brisk jaw jerk, pout
- Gait instability especially on turning

Ophthalmology Review



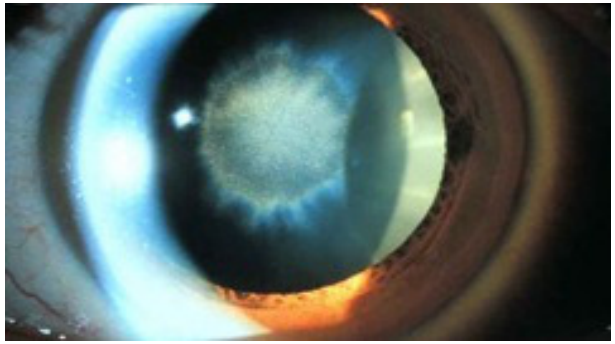
Kayser-Fleischer ring

- Deposition of copper in Desçemet's membrane of the cornea
- Confirmed on slit-lamp exam

Kayser-Fleischer rings

Clinical Hallmark of Wilson's disease

- Present in 95% patients with neurological symptoms
- 50% patients with liver disease
- Not pathognomonic for WD, may be found in patients with chronic cholestatic diseases including children with neonatal cholestasis
- ***Sunflower cataracts:*** Rare, caused by deposits of copper in the center of the lens, slit lamp examination

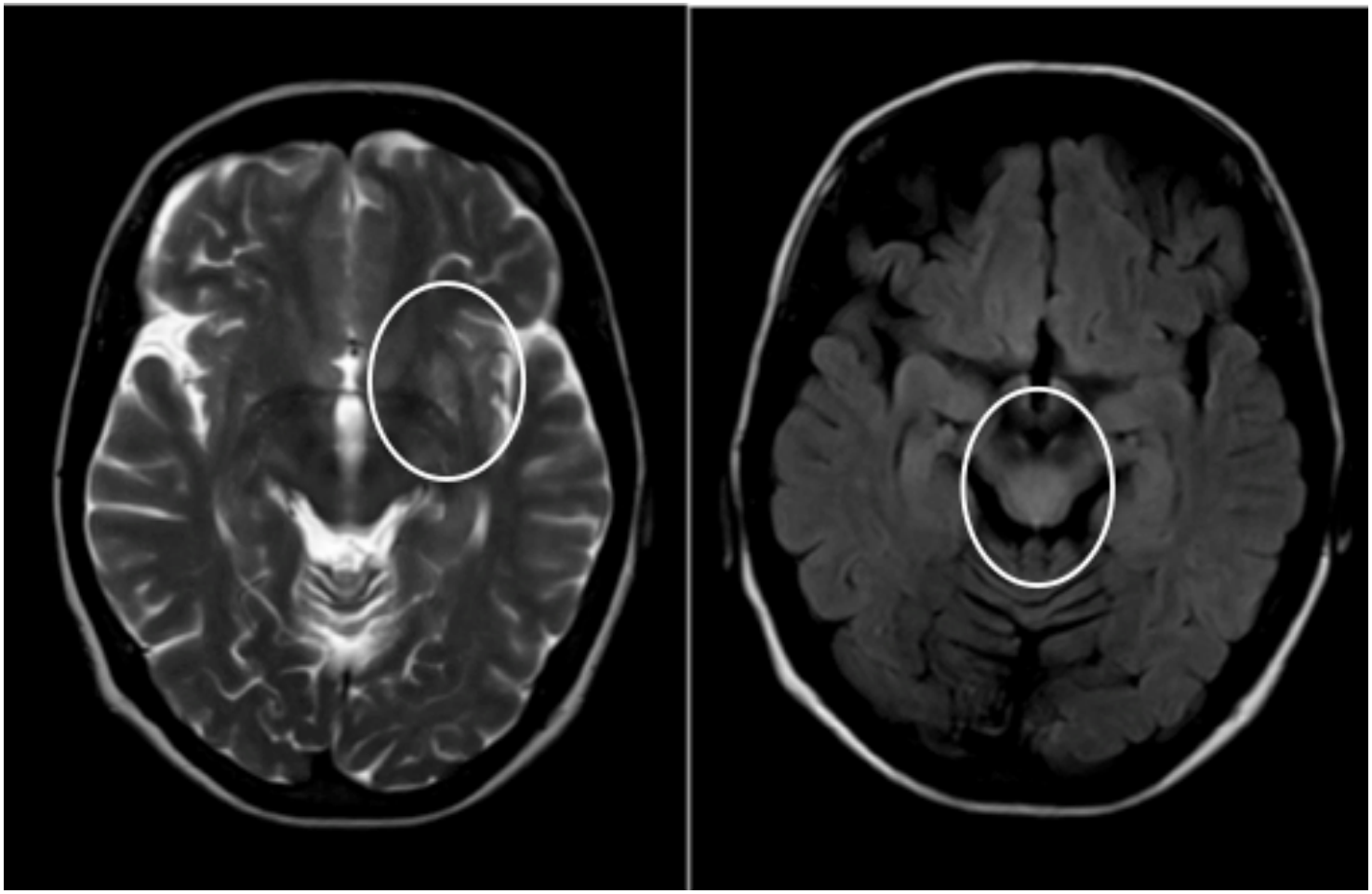


Gastroenterology 1997;113:212; Gut 2000;46:415; Br Med J 1969:3:95

	INVESTIGATIONS : 2012
FBC	• Hb 11.5 MCV 88 WCC 3.3 Platelets 158
CEU	• Na 143 K 4.0 Urea 4.1 Creatinine 79 • No proteinuria • 24hr urine Creatinine Clearance = 74 ml/min
LFT	• **TB 34 Conj Bil 11** ALP 71 GGT 19 ALT 15 AST 37 • **LDH 632** • INR 1.4 Albumin 38 • Ammonia 25
Copper	• Serum copper 5.1 umol/L (12.6 – 24.3) • Ceruloplasmin 0.1 g/L (0.2 – 0.6) • 24 hour urinary copper: 5 umol/L

Gastroscope: Grade 1 varices

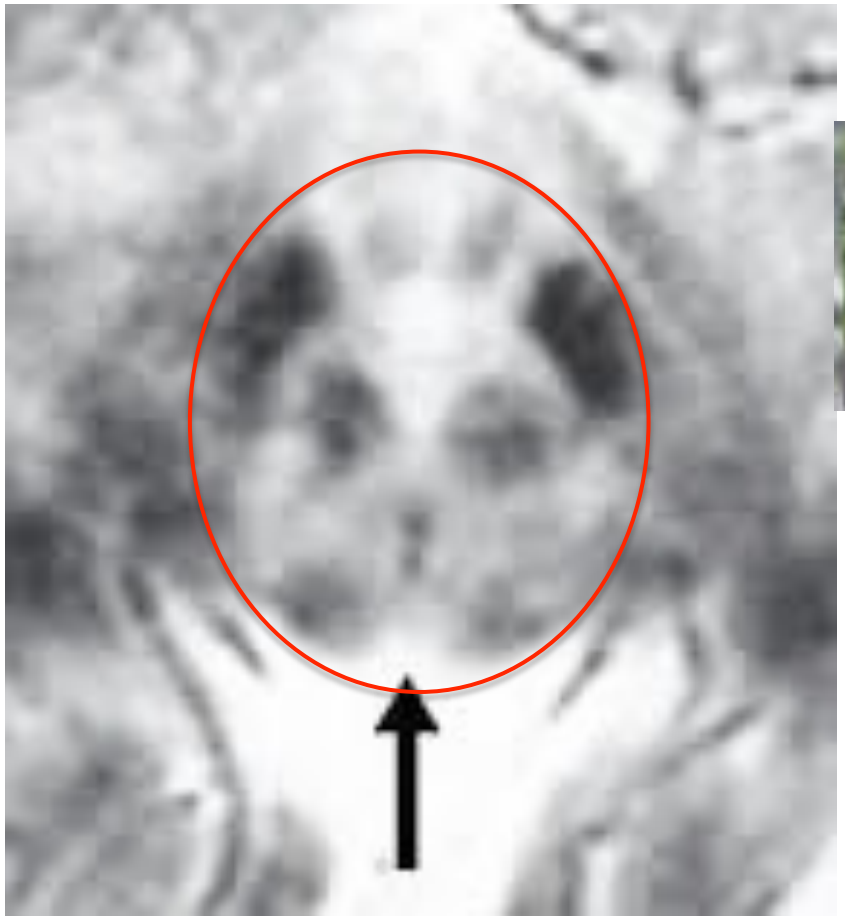
MRI Brain



Left: ***T2 weighted axial image*** demonstrating asymmetric hyperintense signal of the right basal ganglia area

Right: ***Flare image*** demonstrating abnormal hyperintense signal in the midbrain

MRI : Face of Giant Panda



Mov Disord 2008;23:1560; Neurology 2003;61:969; Mov Disord 2010;25:672

Case Summary

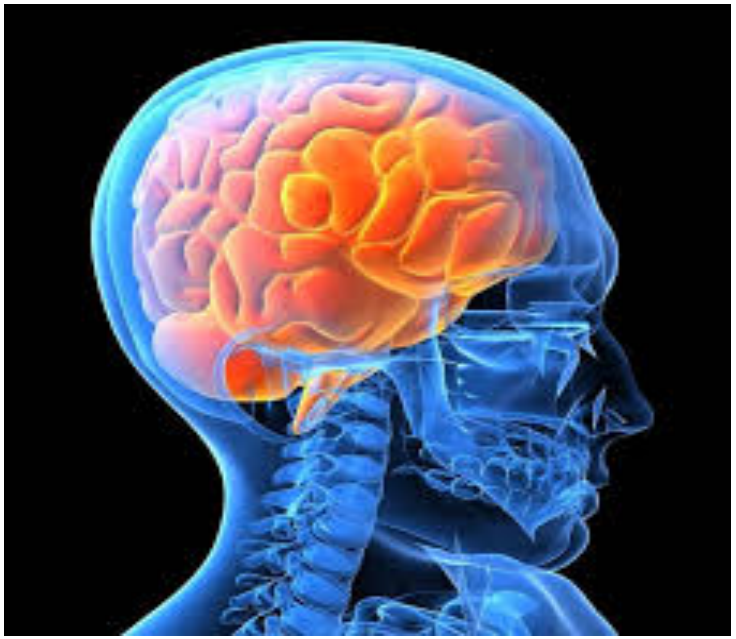
35 year old mother, presented with decompensated liver disease at age 20, diagnosed with Wilson's Disease

- Commences D-penicillamine → compensated cirrhosis
- Discontinues treatment for 4 years (2 pregnancies)
- Restarts D-penicillamine until 2010: No longer accessible in SA
- Presents with Neurological Wilson's disease in 2012, but her liver disease remains well compensated - inadequate Zinc dosage

Role of Liver Transplantation:

- Not indicated at this stage: Liver disease well compensated
- Main issue is inadequate therapy
- Variable results for neurologic WD
  - Some reports of improving established neurological dysfunction
  - Others report neurological deterioration

Neurological
Wilson's Disease

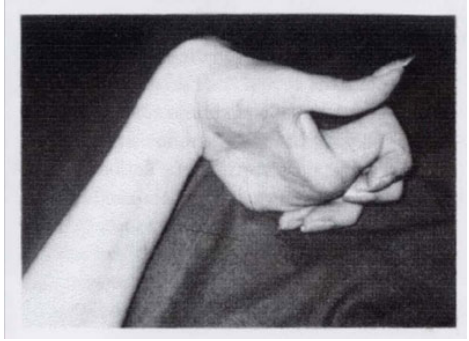


Neurological Wilson's Disease

- **Walshe:** *"No two patients with WD are the same, even in a sibling relationship, and that there is no such thing as a typical picture of Wilson's disease"*
- Neurological symptoms & signs of Wilson's Disease are very variable
- **Spectrum:** Neurological, behavioral and psychiatric
  - Subtle and intermittent for many years
  - Develop very rapidly, progressing to complete disability within months
- Most data is from large case series:
  - Mean age of onset range from about 15–21 years of age
  - Neurologic manifestations at initial presentation have been reported in approximately 18–68% of cases
- Unified Wilson's Disease Rating Scale (UWDRS): assess severity

Semin Neurol 2012; 32(05): 538; Ann N Y Acad Sci. 2010;1184:173; Parkinsonism Relat Disord. 2011;17(7): 551; Mov Disord 2008;23:54; Neurol Neurochir Pol 2007;41:1

Clinical Features



Clinical categories that encompass the majority of neurologic WD

- Dystonic syndrome : 11- 65% - focal, segmental or generalised
- Ataxia : 22-55%
- Pseudosclerosis (tremor +/– dysarthria) : 85–97%
- Akinetic-rigid syndrome (Parkinsonian) : 19–62%
- Tremor : “wing-beating appearance”
- It is not uncommon for just a single manifestation to be present initially… with disease progression, complex combinations co-exist… with a small subset of features that will predominate
- **Other features include:** Chorea, athetosis, myoclonus, seizures, drooling and eye movement abnormalities

Bed bound and unable to care for themselves

Neurological WD: Psychiatric features

- **Initially may be the sole manifestation of WD**
- Present in 30-50% cases – prior to a diagnosis of WD – leading to diagnostic & treatment delay
- **Most commonly reported**: personality changes, incongruous behavior, irritability, impulsiveness, labile mood
- Depression: 20-30%
- Psychosis uncommon feature
- **More common with neurologic WD** and are uncommon in the hepatic presentation

Clin Neuro psychol 2004;17:367; Parkinsonism Relat Disord 2009;15:772

Therapeutic options

D-Penicillamine : Copper chelator

- Increases hepatic Cu ligand, metallothionein
- Major effect is to promote the urinary excretion of copper
- **Side-effects numerous**
  - Fever and rash
  - Nausea, vomiting and anorexia
  - Aplastic anaemia
  - Proteinuria ➔ nephrotic syndrome
- **Neurological Wilson's Disease: Deemed not safe**
  - Worsening of neurologic symptoms has been reported in 10–50% patients treated with D-penicillamine during the initial phase of treatment
  - Neurological deterioration may not be reversible
- **Pregnancy** – not proven to be safe, but significant risk of disease progression if therapy is stopped
- Once in stable phase of disease – reduce dose & administer Zinc as maintenance therapy

Therapeutic options

Trientine: Copper Chelator

- Considered first line therapy
- Promotes urinary copper excretion
- Decreases intestinal copper absorption
- Neurological worsening after beginning of treatment with trientine has been reported, but appears less common than with penicillamine
- ***Side-effects:*** Gastritis and iron deficiency anaemia
- Not available in SA
- Access via MCC section 21 application

Ammonium tetrathiomolybdate

- Still an experimental drug, not routinely available, and its long-term safety and efficacy is unknown

Therapeutic options

Zinc

- Zinc acetate preferred over zinc sulphate
  - 150mg elemental Zinc/day
- Induces enterocyte metallothionein that has a higher affinity for copper than zinc
- Net effect is to bind copper present in the enterocyte and inhibit absorption
- Copper is not absorbed but is lost into the fecal contents as enterocytes are shed by normal turnover
- Induces hepatocyte metallothionein and binds toxic Copper in liver
- Used in maintenance after urinary Cu excretion <500ug/day

Treatment Targets

Recommended Target Result Ranges for Good Copper Control in Treated Wilson Disease Patients

24 Hour Urine Copper

- **On Chelators**: 200 - 500µg (3 - 8µmol)/day
- **On Zinc**: <75µg/day

24 Hour Urine Zinc

- >2.0mg/day

Non-Ceruloplasmin in Bound (Free) Copper

- 5 - 15 µg/dl

LAB TRACKER - COPPER CALCULATOR

Serum Copper (mcg/dl)	Ceruloplasmin (mg/dl)	Non-Ceruloplasmin Copper	
			Calculate

Serum Copper (micromoles/liter)	Ceruloplasmin (mg/L)	Non-Ceruloplasmin Copper	
			Calculate

Copper Concentration (micromoles/liter)	Volume (liters)	Copper per 24 hours (micrograms)	
			Calculate

Copper concentration (mcg/dl)	Volume (liters)	Copper per 24 hours (micrograms)	
			Calculate

Copper concentration (mcg/liter)	Volume (liters)	Copper per 24 hours (micrograms)	
			Calculate

Zinc concentration (mcg/liter)	Volume (liter)	Zinc per 24 hours (micrograms)	
			Calculate

Wilson Disease Association: Online Calculator

Retrospective study (2002 to 2015), 17 patients LT for Neurological WD (Abstract 134 AASLD 2016)

- Main neurological symptoms combined dystonic postures (15/17), parkinsonian syndrome (9/17) and tremor (3/17)
- **Mean age at diagnosis of WD was 17.9 [6-39] yrs**
- Interval time between neurological worsening and LT was 12.6 [3-24] mnths
- Mean age at LT was 20.2 [11-41] years : All Child A cirrhosis
- Mean follow-up time post LT was 51.8 [3-156] mnths
- **Survival was 84%, 75% and 66% at 1, 2 and 5 years respectively**
- 4 patients died after LT from severe sepsis, after an interval of 16 [1.5-36]
  - All had a severe sepsis with a stay in intensive care unit before LT
- **12 pts (70%) needed nutritional support (gastrostomy or jejunostomy) & 9 (53%) a tracheotomy** in a context of swallowing disorders
- All of patients alive presented an improvement after LT
- **Mean percentage of improvement of UWDRS: 61.2% (±22.2)**
  - 6 pts (35%) - major improvement (>70%)
  - 5 pts (29%) - moderate improvement (30% to 70%)
  - 2 pts (12%) - mild improvement (<30%)

Our Patient

2016 : 4 years of Trientine therapy

Liver Disease: Remains compensated

- Normal synthetic function
- No ascites and no variceal bleeds

Neurological Manifestations: No progression

- Less emotionally labile
- Dysarthria has improved
- Cogwheel rigidity and tremor improved
- Gait has normalised

Lifelong Trientine therapy