Wilson’s Disease
A 20 year old woman’s 15 year journey

CWN Spearman

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Department of Medicine
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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

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.

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

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

<table>
<thead>
<tr>
<th>BIOCHEMISTRY</th>
<th>Normal</th>
<th>Wilson’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Total Serum Copper (ug/dl)</td>
<td>80-140</td>
<td>&lt;80</td>
</tr>
<tr>
<td>• Urine Copper (umol/24 hrs)</td>
<td>0.2-0.8</td>
<td>&gt;1.6</td>
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<tr>
<td>• Serum Caeruloplasmin (g/L)</td>
<td>&gt;0.2</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>• Hepatic Copper (ug/gram dry weight)</td>
<td>15-40</td>
<td>250-3000</td>
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</table>

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

Wilson's Disease: Diagnosis

<table>
<thead>
<tr>
<th>LIVER DISEASES</th>
<th>HEPATIC COPPER LEVELS (ug/gram dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normal</td>
<td>30</td>
</tr>
<tr>
<td>• Wilson's Disease</td>
<td>730</td>
</tr>
<tr>
<td>• Primary Biliary Cholangitis</td>
<td>410</td>
</tr>
<tr>
<td>• Primary Sclerosing Cholangitis</td>
<td>245</td>
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<tr>
<td>• Extrahepatic Obstruction</td>
<td>130</td>
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<tr>
<td>• Alcoholic/Cryptogenic cirrhosis</td>
<td>40</td>
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</tbody>
</table>

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

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**

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

<table>
<thead>
<tr>
<th>Typical clinical symptoms and signs</th>
<th>Other tests</th>
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<tbody>
<tr>
<td>KF rings</td>
<td>Liver copper (in the absence of cholestasis)</td>
</tr>
<tr>
<td>Present</td>
<td>&gt;5x ULN (&gt;/=4 μmol/g)</td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic symptoms**</td>
<td>0.8-4 μmol/g</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>Normal (&lt;0.8 μmol/g)</td>
</tr>
<tr>
<td>Absent</td>
<td>-1</td>
</tr>
<tr>
<td>Serum ceruloplasmin</td>
<td>Rhodanine-positive granules*</td>
</tr>
<tr>
<td>Normal (&gt;0.2 g/L)</td>
<td>1</td>
</tr>
<tr>
<td>0.1-0.2 g/L</td>
<td></td>
</tr>
<tr>
<td>&lt;0.1 g/L</td>
<td></td>
</tr>
<tr>
<td>Coombs-negative hemolytic anemia</td>
<td>Urinary copper (in the absence of acute hepatitis)</td>
</tr>
<tr>
<td>Present</td>
<td>Normal</td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
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<td>1-2x ULN</td>
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<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;2x ULN</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Normal, but &gt;5x ULN after D-penicillamine</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Mutation analysis</td>
<td></td>
</tr>
<tr>
<td>On both chromosomes detected</td>
<td></td>
</tr>
<tr>
<td>On 1 chromosome detected</td>
<td></td>
</tr>
<tr>
<td>No mutations detected</td>
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</table>

**TOTAL SCORE**

<table>
<thead>
<tr>
<th>Evaluation</th>
</tr>
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<tbody>
<tr>
<td>Diagnosis established</td>
</tr>
<tr>
<td>Diagnosis possible, more tests needed</td>
</tr>
<tr>
<td>Diagnosis very unlikely</td>
</tr>
</tbody>
</table>

*If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging. KF, Kayser-Fleischer; ULN, upper limit of normal.
Diagnostic Algorithm: Leipzig score

Typical clinical symptoms (extra pyramidal symptoms, KFR, CPL)

- Score 0-1
  - Urinary copper >1.6 µmol/d
    - Hepatic copper
      - Normal or <4 µmol/g
      - Score ≤3

- Score 2-3
  - Urinary copper >1.6 µmol/d
    - >4 µmol/g
    - Score ≤3

- Score ≥4
  - Diagnosis established
    - Mutation analysis
      - 2 mutations
      - 1 mutation
      - 0 mutation

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

<table>
<thead>
<tr>
<th></th>
<th>1*</th>
<th>2*</th>
<th>3*</th>
<th>4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (µmol/L)</td>
<td>100-150</td>
<td>151-200</td>
<td>201-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>100-150</td>
<td>151-300</td>
<td>301-400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>INR</td>
<td>1.3-1.6</td>
<td>1.7-1.9</td>
<td>2.0-2.4</td>
<td>&gt;2.4</td>
</tr>
<tr>
<td>WBC [10⁹/L]</td>
<td>6.8-8.3</td>
<td>8.4-10.3</td>
<td>10.4-15.3</td>
<td>&gt;15.3</td>
</tr>
<tr>
<td>Albumin [g/L]</td>
<td>34-44</td>
<td>25-33</td>
<td>21-24</td>
<td>&lt;21</td>
</tr>
</tbody>
</table>

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**: 1\textsuperscript{st} 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
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

## INVESTIGATIONS : 2012

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>FBC</strong></td>
<td>Hb 11.5 MCV 88 WCC 3.3 Platelets 158</td>
</tr>
</tbody>
</table>
| **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
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

References:
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

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

<table>
<thead>
<tr>
<th>Serum Copper (mcg/dl)</th>
<th>Ceruloplasmin (mg/dl)</th>
<th>Non-Ceruloplasmin Copper</th>
<th>Calculate</th>
</tr>
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<table>
<thead>
<tr>
<th>Serum Copper (micromoles/liter)</th>
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<thead>
<tr>
<th>Copper Concentration (micromoles/liter)</th>
<th>Volume (liters)</th>
<th>Copper per 24 hours (micrograms)</th>
<th>Calculate</th>
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</table>

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

**Wilson Disease Association: Online Calculator**
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] mths

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] mths

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] mths
  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
Health Disparities: sub-Saharan Africa

Burden of liver disease in sub-Saharan Africa is substantial

Challenges

- Lack of data to accurately establish disease prevalence
- Lack of access to health facilities - diagnostic and interventional
- Access and cost of medications

Apply similar programmes to HIV/AIDS to combat liver disease in SSA
- PEPFAR
- Global Fund to Fight AIDS, TB and Malaria

→ brought medication at affordable prices to SSA