Wilson disease—an update for 2014
Enfermedad de Wilson. Actualización

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Key points—Wilson disease

• Wilson disease is rare, maybe hard to diagnose, but highly treatable with good outcomes in patients who tolerate and adhere to treatment.

• The Wilson ATPase (gene product of ATP7B) has two actions in the liver cell: production of ceruloplasmin containing Cu molecules, and biliary excretion of copper.

• Basal 24-hr urinary Cu excretion is an excellent clinical test for Wilson disease; new biomarkers are desirable.

• Genetic diagnosis is conclusive, but complicated, also expensive.

• Treatment must be individualized.
Homage to the giants

Sir William Osler

Dr. Kinnear Wilson

Sir Archibald Garrod
Typical patient from Wilson’s own paper

E.P. in his school days

He presented clinically with psychiatric symptoms resembling schizophrenia at 17 years-old. Then later he developed neurological findings: tremor, drooling, difficulty swallowing.

E.P. in June 1910 “Note vacant expression, open mouth, sialorrhea, contractures. (Exposure 1/250 second to counteract effect of constant tremor.)”

He died 4 mos later, aged 21 yrs, and never had any signs or symptoms of cirrhosis.

Wilson Brain 1912;34:295
Wilson’s photos of E.P.’s liver

- Rather lighter in colour than usual
- No bile-staining
- Average size of the nodules “perhaps that of a three-penny piece”
- No ascites
- No evidence of hepatitis

Wilson Brain 1912;34:295

Bilateral symmetrical atrophy and degeneration of the lenticular nuclei; internal capsules intact; thalamus normal bilaterally.
What Wilson actually said

What must be considered, as it seems to me, the most curious and the most remarkable feature of this familial nervous disease is the constant presence of a profound degree of cirrhosis of the liver. This hepatic cirrhosis does not reveal itself by any symptoms during life, nevertheless it is always found after death. It is mixed in type, as will be subsequently shown. Syphilis and alcohol, as possible morbific agents in connexion with this cirrhosis, can, I believe, be entirely excluded. This association, in young people, of cirrhosis of the liver with bilateral symmetrical softening of the lenticular nucleus constitutes the disease from the pathological standpoint; clinically, the symptoms are exclusively nervous.

Wilson Brain 1912;34:295
Why is Wilson disease problematic?

It is rare: 1 per 30,000 population (on average). Clinical diagnosis can be difficult. Medical treatment is life-saving but needs to be started without undue delay.

Paradoxical features get in the way of diagnosis:

• It is a copper-overload disease.
• Serum copper is low.

How can this be? Especially because it is autosomal recessive, one-gene defect.

Identifying the gene abnormal in Wilson disease and studying its gene product solved this problem:

The protein deranged in Wilson disease does more than one thing inside the cell.
Case report—1

• 12 year-old female, recent immigrant from the Canary Islands, referred because of abnormal LFTs
• Always healthy, and her brothers and sisters are also healthy
• Recent brief bout of jaundice, no dark urine: GP thought Gilbert syndrome but checked LFTS which were elevated (therefore not Gilbert—so referral)
• Physical exam: looks well, BMI on 75%ile, free of jaundice but liver edge palpable and spleen can be tipped; no obvious neurological abnormalities
• Liver sonography shows bright liver, with ?? coarse pattern, and confirms spleen enlargement
Case report—laboratory data

• CBC: entirely normal
• AST 90 U/L; ALT 66 U/L; ALP normal for age
• Albumin 34 g/L; T bilirubin 34 μmol/L; C bilirubin 22 μmol/L
• INR 1.3
• Virological screening for CHB and CHC negative
• IgG 14.1; non-specific autoantibodies negative
• It’s reasonable essential to investigate genetic-metabolic disease .........................
Case report—‘copper studies’

• Serum ceruloplasmin 60 mg/L
• Serum copper 0.27 µmol/L
• Basal 24-hr urinary Cu excretion: 1.7 µmol/d
• No Kayser-Fleischer rings by slit-lamp exam
• Liver biopsy: fibrosis, little inflammation, Cu stain negative
• Liver parenchymal Cu: 400 µg/g dry wgt
• Genotype: L708P/M769V
• So this is a case of Wilson disease ............
Suppose—“copper studies”

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**Classic versus updated diagnostic criteria**

**Classic criteria**

1) Patient with liver or neurological disease
2) Age range: 7-35 years-old
3) Kayser-Fleischer rings present
4) Very low serum ceruloplasmin (<50 mg/L)

**Updated criteria**

1) No change—note sporadic jaundice due to hemolysis
2) Virtually any age: 1-80s
3) K-F rings: adults: 60%; children: 40%; more likely with neurological WD than hepatic WD
4) Serum ceruloplasmin <140 mg/L (but normal serum ceruloplasmin does not rule out WD)
Wilson ATPase (P$_{1B}$-type ATPase)

- Copper-binding Domain (comprised of six copper-binding units)
- Nucleotide-binding/phosphorylation domain
- Actuator domain
- Transduction Domain
- lumen
- cytoplasm
- membrane

- Copper-binding Domain (comprised of six copper-binding units)
- Nucleotide-binding/phosphorylation domain
- ‘ATP Engine’
What does the Wilson ATPase do?

- Clinical findings in Wilson disease:
  - Overload of copper in the liver.
  - Low serum ceruloplasmin (protein is abnormal: does not contain copper).

- **Wilson ATPase does at least 2 things:**
  - Plays a role in the incorporation of copper into ceruloplasmin
  - Expedites biliary excretion of excess copper

- Net effect is removal of copper from liver

- Cell physiology studies indicate a further broad function: sensing the available copper within a hepatocyte
ATP7B (13q.14) mutations

>500 mutations have been identified at the present time

- Mutations mainly point mutations, unlike those in Menkes disease
- Approximately 80% of patients are compound heterozygotes (two different mutations → clinical disease)

Classifying \textit{ATP7B} mutations
Diagnosing Wilson disease

• Basal 24-hour urinary copper excretion

  What is interesting here:
  • n=40, but test not done in 2 (both < 4 years-old) — So n=38
  • 5 children with excretion < 0.6 were <4 years-old
  • Thus excluding those basal 24-hr urinary Cu excretion was >0.6 in 30/33 or 91%

Figure from Nicastro et al. Hepatology 2010;52:1948

• Genetic investigation
Basal 24-hr Cu excretion highly informative if cut-off set *low enough*

**Utility of basal 24-hr urinary Cu at >0.6 µmoles/day:**

- **27 of 29** in Toronto series (Roberts et al, JPGN 2004;39(Suppl 1):S128; see also Hepatology 2008; 47:2089)
- **161 of 162** in Heidelberg series, mainly adults (Merle et al, Gut 2007;56;115)
- **Optimal** in Naples paediatric series (n=40): sensitivity 79% [CI 73-93%] and specificity 88% [CI 77-95%] (Nicastro et al, Hepatology 2010;52:1948)
- **Alternatively,** ROC analysis favourable for cut-off at 0.8 µmoles/day in children (Lu et al, Zhonghua Gan Zang Bing Za Zhi 2010;18:49)
Diagnosing Wilson disease

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• Genetic investigation
  • Genotype or similar: methods improved/improving
  • Family studies: all first-degree relatives, not just siblings
Case—treatment options

• D-penicillamine (chelator; covered by 3rd-party payers) \(\leftarrow\) “first-line treatment” but lots of adverse effects

• Trientine (safer chelator; highly effective but relatively expensive—not always covered by 3rd-party payers) \(\leftarrow\) “second-line treatment” can be lifesaver

• Zinc (not a chelator; cheap) \(\leftarrow\) problems with adherence because of three times per day dosage

• Antioxidants (for example, vitamin E) \(\leftarrow\) no proven benefit yet
D-penicillamine contrasted to trientine

This ‘SH’ group is what captures the Cu.

These chemical structures show just how different these two drugs are—a reason trientine can be substituted for D-penicillamine when adverse effects occur.

Trientine action depends on its 3-D structure!
Case—treatment strategy

- D-penicillamine: start incrementally, monitor for side effects; if fever, cytopenias, proteinuria, or severe skin disorder—switch to trientine or zinc
- Trientine: could start with trientine if obvious risk of adverse side effect from D-penicillamine such as renal dysfunction or bone marrow disorder already present
- Zinc: monitor zinc status and adherence; note that actual zinc salt less important than production standards of pharmaceutical manufacturer; monitor LFTs
- Specifics of monitoring well-described in available practice guidelines

- General approach, especially for hepatic WD: chelator for 1-5 years, then consider maintenance with zinc monotherapy
- Alternative approach, especially for neuro-WD: use zinc as primary Rx
- Possible approach: zinc as primary Rx in asymptomatic children with WD
Recent questions about zinc

• German-Austrian report: 288 patients, median follow-up 17 years (0.4-54 years), only 23 Zn monotherapy (Gastroenterology 2011;140:1189)
  – Some primary non-responders
  – Late treatment failures, 15+ years after diagnosis

• Dutch report: 17 patients, median follow-up 14 years (2-30 years) (Hepatology 2009; 50:1442)
  – Hepatic WD did worse than neuro WD
  – Hepatic disease worsened in some neuro WD patients

• Scattered older reports suggesting zinc not effective or else toxic

• Multiple lines of evidence indicate that zinc does not remove copper from liver parenchyma.
Possible mechanisms of zinc treatment failure
Chronic zinc Rx in Wilson disease

- Need to monitor for hepatic deterioration (follow AST, ALT)
- If deterioration, switch back to chelator.
- Nevertheless—indications for zinc:
  - Neurological presentation
  - Very young child
  - Extremely insecure diagnosis
- Treating WD with zinc is not being on auto-pilot!
Summary—2014

• **Wilson disease may be less rare than we think.** It can be hard to diagnose. Early diagnosis is best. Patients who tolerate and adhere to treatment generally enjoy good health and normal life-span.

• The Wilson ATPase (gene product of \textit{ATP7B}) has two actions in the liver cell: production of ceruloplasmin containing Cu molecules, and biliary excretion of copper. This accounts for the ‘paradoxical’ findings.

• Basal 24-hr urinary copper excretion is an excellent clinical test for Wilson disease so long as patient can collect urine. New biomarkers are desirable.

• **Genetic diagnosis is conclusive.**

• **Treatment must be individualized.** Chelation first then maintenance with zinc seems like best plan, but other strategies may be needed in some patients.
Thank you!
Muchas gracias!