Wilson Disease - Our Experience

Hussein Shamaly M.D.

Pediatric Gastroenterology Unit
Pediatric Department
French Hospital, Nazareth

Clalit Health Services
Key Concepts

- Wilson disease is more often considered than found, but if not considered will not be found.
- Prevalence 1:30,000
- Rarely before 3-4 y old. Usually appears II – IV decade
- WD should be considered in the D.D. of any unexplained liver disease, especially in these with liver disease & neurological or psychiatric symptoms.
Key Concepts

- Gene encodes a p-type ATP-ase **ATP7B**.
- It is responsible for copper excretion in bile and copper incorporation in ceruloplasmin
- Biliary copper excretion
- Hepatic copper accumulation
- Copper deposition in extra hepatic sites

Pathophysiology related to copper overload
Human Copper Metabolism

Body Content 100 mg Copper

Liver
- Storage 20 mg
- Excretion
  - Export
  - Blood 10 mg

Ceruloplasmin 4.3 mg
- Albumin / Histidine 0.2 mg
- RBC 5.5 mg
- SOD

Brain 20 mg
- Muscle 35 mg
- Kidney 5 mg
- Connective Tissue 10 mg

Dietary Copper 5 mg/day
- Duodenum
- Feces (4.9 mg/day)
- Urine (<0.1 mg/day)
Ceruloplasmin

- 132 kd protein, synthesized in liver.
- Acute phase reactant, copper carrying protein.

**Increased**
- Inflammation
- Neonatal period
- Hyperestrogenemia
- Pregnancy
- Oral contraceptive

**Decreased**
- Aceruloplasminemia
- Renal disease
- Enteric loss
- End stage liver disease
- Copper deficiency
- Early infancy
Indications for Testing

- Unexplained abnormal liver enzymes
- Unexplained hemolysis
- Neurological disturbances
- Fanconi’s syndrome
- Hypouricemia
- Keiser- Fleishner ring
- Siblings of affected patients
Clinical Features

- Hepatic (50%)
- Neurologic (40-50%)
- Psychiatric (10-25%)
- Hemolytic anemia (15%)
- Renal – Fanconi’s syndrome (rare)
Hepatic Manifestations

- Hepatomegaly
- Elevated liver enzymes
- “Recurrent” hepatitis
- Chronic Active hepatitis
- Cirrhosis
- portal hypertension
- Acute liver failure, fulminant hepatitis
Neurologic Manifestations

- Movement disorders: tremor & chorea
- Dystonia
- Pseudobulbar palsy
- Seizures
- Hypokinesis
- Drooling
- Dysarthria
Psychiatric Manifestations

- Personality disturbances
- Depression
- Neurosis
- Psychosis
Other Systems

- Blood - hemolytic anemia
- Renal – aminoaciduria, nephrolithiasis
- Skeletal – osteoporosis, arthritis
- Cardiac – cardiomyopathy, dysrhythmias
- GYN – infertility, amenorrhea, repeated miscarriages
- Pancreatitis
- Hypoparathyroidism
Wilson Disease

Diagnosis
## Diagnosis of Wilson Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Wilson’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Copper (micgm/dl)</td>
<td>80-140</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Urine Copper (mcg/24 hr)</td>
<td>&lt;40</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Serum ceruloplasmin (mg/dl)</td>
<td>20-40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Hepatic copper (micg/gm dw)</td>
<td>15-50</td>
<td>250-3000</td>
</tr>
</tbody>
</table>

- **Serum Free-Copper Concentration**
  - Total Cu - Ceruloplasmin X 3.15
  - Free Cu usually < 100 μg/L
  - Wilson’s Disease: Free Cu > 200 μg/L
<table>
<thead>
<tr>
<th>Mean Hepatic Cu (mcg/gr dry weight)</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>730</td>
<td>Wilson’s Disease</td>
</tr>
<tr>
<td>410</td>
<td>Primary Biliary Cirrhosis</td>
</tr>
<tr>
<td>245</td>
<td>Primary Sclerosing Cholangitis</td>
</tr>
<tr>
<td>130</td>
<td>Extra hepatic Biliary Obstruction</td>
</tr>
<tr>
<td>1830</td>
<td>Indian Childhood Cirrhosis</td>
</tr>
<tr>
<td>40</td>
<td>Alcoholic /Cryptogenic Cirrhosis</td>
</tr>
<tr>
<td>30</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Kayser-Fleischer Ring
Wilson Disease

Macro and micorvesicular steatosis
Wilson Disease

Copper stain (rhodanine)

Atlas of the Liver 2nd edition
MRI

Deposition of Copper in the Basal Ganglia

Wilson Normal
Genetic Test

- Large gene & protein
- >200 mutation
- Compound heterozygote
- Homozygote
Treatment

- Lifelong treatment
- Asymptomatic & active disease
- Diet
- D-Penicillamine
- Trientine
- Zinc
- Ammonium tetrathiomolybdate

Liver Transplantation
Diet: Eliminate Copper

Rich Diet

- Organ meats
- Shellfish
- Nuts
- Chocolate
- Mushrooms
- Dried fruits or beans
- Water supply
D-Penicillamine

- General chelator
- Induce cupriuria
- Induce metallothionein
- Well absorbed, meal decrease absorption

**Monitoring**: urinary copper 250-500ug
- Normalization of nonceruloplasmin-copper
D-Penicillamine Side Effects

- Neurologic deterioration at initial treatment - common
- Hypersensitivity reaction: fever, rash, lupus like
- Bone marrow suppression: aplastic anemia, leukopenia, thrombocytopenia
- Renal: Nephritis, nephrosis
- Dermatologic: interferes with collagen synthesis - Degenerative changes, wound healing
- Hepatotoxicity
Trientine

- General chelator; induces cupriuria
- Better safety profile than penicillamine
- Ideal drug to Pt with penicillamine intolerance
- Poorly absorbed
Trientine

Side effects:
- Neurologic deterioration at initial treatment – rare
- Gastritis

Rare side effects
- Aplastic anemia
- Sideroblastic anemia
Zinc

Mode of action:
- Metallothionenin inducers
- Blocks intestinal absorption of copper

Usage:
- For asymptomatic, maintenance pregnancy and in combination therapy
Zinc

No neurologic deterioration
Poorly absorbed with food

**Side effects:**

- Gastric irritation, Gastritis
- Pancreatitis – biochemical
- Zinc accumulation
- Possible change in immunologic function

**Monitoring:** urinary copper < 75ug, normalization of nonceruloplasmin- copper
**Mode of action:**
- General chelator
- Blocks intestinal absorption of copper
- Induces intestinal and urinary copper loss

**Side effects:**
- Anemia
- Neutropenia
Fulminant Hepatic Failure

May cause fatigue, hepatic insufficiency, extreme jaundice (because of accompanying hemolysis), severe coagulopathy, ascites, hepatic coma, renal failure and death if liver transplantation is not performed.

Interventions to reduce secondary organ injury while awaiting a suitable donor organ: albumin dialysis, plasmapheresis, exchange transfusion.

Liver transplant remains the treatment of choice for fulminant hepatic failure.
Our Patients

- 7 children with elevated liver enzymes which were found in routine blood testing
- 3 of them were diagnosed as WD
- No patient was found with hepatic, neurological, psychiatric or hemolytic manifestations
- Clinical examination – normal
Laboratory Tests

Viral:
- HBsAg
- HCV Ab
- HAV Ab
- EBV IgM
- CMV IgM

Immunologic:
- Immunoglobulins
- Antiparietal cell Ab
- Anti mitochondrial Ab
- Anti smooth muscle Ab
- ANA
- LKM
- Anti endomesial Ab
- AFP
<table>
<thead>
<tr>
<th>Abed</th>
<th></th>
<th>Moad</th>
<th>Nur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>5</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Relatives with Wilson</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>AST (u/l)</td>
<td>95</td>
<td>159</td>
<td>170</td>
</tr>
<tr>
<td>ALT (u/l)</td>
<td>125</td>
<td>90</td>
<td>125</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td>N</td>
<td>Fatty liver</td>
</tr>
<tr>
<td>Ceruloplasmin(mg/dl)</td>
<td>18</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Cu in serum (mcg/l)</td>
<td>95</td>
<td>85</td>
<td>26</td>
</tr>
<tr>
<td>Cu in urine (24h) ( mcg/l)</td>
<td>171</td>
<td>330</td>
<td>106</td>
</tr>
<tr>
<td>Cu after penicillamin (mcg/l)</td>
<td>575</td>
<td>4800</td>
<td>477</td>
</tr>
<tr>
<td>Keiser-Fleisher ring</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Liver histology: Steatosis</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Orcein</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rhodenin</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cu in liver( mcg/gr dry weight))</td>
<td>940</td>
<td>1520</td>
<td>1480</td>
</tr>
<tr>
<td>Genetics</td>
<td>Moad</td>
<td>Nur</td>
<td>Homoz LECOR</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>1480</td>
<td>-</td>
</tr>
<tr>
<td>90</td>
<td>F</td>
<td>1480</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>1480</td>
<td>-</td>
</tr>
<tr>
<td>Adham</td>
<td>Hadil</td>
<td>Loay</td>
<td>Ali</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>12.11</td>
<td>9.5</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>28</td>
<td>66</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>64</td>
<td>95</td>
<td>52</td>
<td>73</td>
</tr>
<tr>
<td>US</td>
<td>N</td>
<td>Fatty liver</td>
<td>Fatty liver</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>25</td>
<td>2.5</td>
<td>32</td>
</tr>
<tr>
<td>23.6</td>
<td>129</td>
<td>148</td>
<td>15</td>
</tr>
<tr>
<td>110</td>
<td>168</td>
<td>45</td>
<td>140</td>
</tr>
<tr>
<td>140</td>
<td>760</td>
<td>645</td>
<td>904</td>
</tr>
<tr>
<td>456</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Keiser-Fleisher ring</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver histology: Steatosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Orcein</td>
<td>37</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rhodenin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>48</td>
<td>Cu in liver (mcg/gr dry weight)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Age(year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>9.5</td>
<td>12.11</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>AST(u/l)</td>
<td>43</td>
<td>66</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>95</td>
<td>31</td>
</tr>
<tr>
<td>ALT(u/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Fatty liver</td>
<td>Fatty liver</td>
<td>Fatty liver</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Fatty liver</td>
<td>Fatty liver</td>
</tr>
<tr>
<td>Ceruloplasmin(mg/dl)</td>
<td>2.5</td>
<td>25</td>
<td>23.6</td>
</tr>
<tr>
<td>Cu in serum(mcg/dl)</td>
<td>148</td>
<td>129</td>
<td>110</td>
</tr>
<tr>
<td>Cu in urine (24h)(mcg/dl)</td>
<td>45</td>
<td>168</td>
<td>140</td>
</tr>
<tr>
<td>Cu after penicillineamin (mcg/dl)</td>
<td>645</td>
<td>760</td>
<td>456</td>
</tr>
<tr>
<td>Keiser-Fleisher ring</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver histology: Steatosis</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Orcein</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rhodenin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Conclusions

- All were asymptomatics
- All were found within normal examination
- All without Keiser-Fleischer ring
- US of Abdomen was not informative, liver mostly fatty
- AST not always > ALT
Ceruloplasmin was low in 2 patients

Ceruloplasmin >20mg% in 1 patients

Cu in serum low in 1 patient. Normal in others

Cu in urine in 24 hours collections is indicative

Cu in urine after penicillamine is indicative
Conclusions - Cont

Liver Histology:

- Most with steatosis
- Orcein stain **Positive** in 1 patient
- Rhodanin stain **Negative**
- Cirrhosis in 1 patient (6 years old)
- Cu level in hepatic tissue is diagnostic
Take Home Message

Consider WD

Do large evaluation

Send to specialist

Early diagnosis & TRT may prevent complications and save lives
thank you
merci
謝謝
danke
Ευχαριστώ
شكرا
どうもありがとうございます
gracias