Metabolic Liver Disease: What’s New in Diagnosis and Therapy?

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• I have nothing to disclose regarding this topic.
Metabolic (Inherited) Liver Disease

- Hereditary hemochromatosis
- Wilson disease
- Alpha-1-antitrypsin deficiency
- Cystic fibrosis
- Others

Classification of Inherited Iron Overload Syndromes

- Hereditary Hemochromatosis
  - HFE-related
    - C282Y/C282Y
    - C282Y/H63D
    - Other HFE mutations
  - Non-HFE-related
    - Hemojuvelin (HJV)
    - Transferrin receptor-2 (TfR-2)
    - Ferroportin (SLC40A1)
    - Hepcidin (HAMP)
    - African iron overload
### Typical Symptoms in Patients with HH

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness, lethargy, fatigue</td>
<td>40-85</td>
</tr>
<tr>
<td>Apathy, lack of interest</td>
<td>40-85</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30-60</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30-60</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>40-60</td>
</tr>
<tr>
<td>Loss of libido, impotence</td>
<td>30-60</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>20-60</td>
</tr>
<tr>
<td>Congestive heart failure symptoms</td>
<td>0-40</td>
</tr>
</tbody>
</table>

### Common Physical Findings in HH

<table>
<thead>
<tr>
<th>Finding</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>60-85</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>50-95</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>40-80</td>
</tr>
<tr>
<td>Arthritis (second, third metacarpophalaneal joints)</td>
<td>40-60</td>
</tr>
<tr>
<td>Clinical diabetes</td>
<td>10-60</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>10-40</td>
</tr>
<tr>
<td>Loss of body hair</td>
<td>10-30</td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td>10-30</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>0-30</td>
</tr>
</tbody>
</table>
## Hereditary Hemochromatosis

### Symptoms and Physical Findings (%)

- No symptoms: 73%
- Lethargy, and/or weakness: 25%
- Loss of libido, impotence: 12%
- Arthralgias: 13%
- Diabetes: 5%
- Skin pigmentation: 5%

*Am J Gastroenterol 92:784-789, 1997*

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### Principal Clinical Features in Hereditary Hemochromatosis

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>34†</td>
<td>35*</td>
<td>163*</td>
<td>37‡</td>
<td>40</td>
</tr>
<tr>
<td><strong>Symptoms (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness, lethargy</td>
<td>73</td>
<td>20</td>
<td>83</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>50</td>
<td>23</td>
<td>58</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>47</td>
<td>57</td>
<td>43</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>Loss of libido, impotence</td>
<td>56</td>
<td>29</td>
<td>38</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Cardiac failure symptoms</td>
<td>35</td>
<td>0</td>
<td>15</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Physical and Diagnostic Findings (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis (biopsy)</td>
<td>94</td>
<td>57</td>
<td>69</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>76</td>
<td>54</td>
<td>83</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>38</td>
<td>40</td>
<td>13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Loss of body hair</td>
<td>32</td>
<td>6</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>12</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td>50</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>82</td>
<td>43</td>
<td>75</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Clinical diabetes</td>
<td>53</td>
<td>6</td>
<td>55</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>

* Patient selection occurred by both clinical features and family screening.
† Only symptomatic index cases were studied.
‡ Discovered by family studies.

The natural history and disease burden of HH

Mutant HFE → Raised SF ± TS → Increased liver iron → Hepatic fibrosis → Iron overload related disease

1 in 200 N.Europeans C282Y +/+ Biochemical Expression 75%

50% 25% 5.6% 1.9% (Cirrhosis)

(Allen et al., Powell et al.)

Survival and causes of death in a cohort of 1086 treated C282Y HFE homozygous patients
Bardou-Jacquet, et al. Rennes - #191

- Variable results on impact of HFE hemochromatosis on survival
- Large cohort of well-defined prospectively documented C282Y homozygotes
- 1,872 C282Y homozygotes prospectively recorded from 1989 to 2009
- Those from 1996 (1,086) selected for this study
- Phlebotomy recommended if ferritin > 300 for men, > 200 for women
Survival and causes of death in a cohort of 1086 treated C282Y HFE homozygous patients
Bardou-Jacquet, et al. Rennes - #191 (continued)

• Mean follow-up 8.7 years
• Overall mortality 0.94 similar to that of the general population
• Ferritin > 2,000 associated with higher mortality while ferritin < 1,000 associated with lower mortality than general population
• Deaths related to liver disease – 51%, mainly from HCC – 76%

Survival and causes of death in a cohort of 1086 treated C282Y HFE homozygous patients
Bardou-Jacquet, et al. Rennes - #191 (continued)

• No increase in cardiac mortality or extra hepatic cancer mortality
• Serum ferritin < 1,000 associated with lower CV and extra-hepatic mortality
• Fibrosis score was highest predictor of death
Survival and causes of death in a cohort of 1086 treated C282Y HFE homozygous patients
Bardou-Jacquet, et al. Rennes - #191 (continued)

- Conclusions:
  - HFE mortality similar to general population
  - However, patients with severe iron overload have increased mortality mainly due to HCC
  - Sustained phlebotomy is beneficial to HH patients

Liver transplantation normalizes serum hepcidin level and cures iron metabolism alteration in HFE Cys282Tyr hemochromatosis.
Bardou-Jacquet, et al. Rennes - #189

- Hepcidin – iron hormone produced in liver effecting iron transport in enterocytes and macrophages
- HH – hepcidin deficiency
- All C282Y homozygous patients who had a LT for complications of HH between 1999-2008
- Iron parameters, hepcidin levels, HIC by MRI performed at end of follow-up
Liver transplantation normalizes serum hepcidin level and cures iron metabolism alteration in HFE Cys282Tyr hemochromatosis.
Bardou-Jacquet, et al. Rennes - #189 (continued)

• Results
  – 18 patients, 56 y.o.
  – Median follow-up 57 months
  – 16 patients for HCC, 1 for liver failure, 1 for biliary hamartomas
  – 16 Child-Pugh – A
  – 1 year survival – 83.3%

• Before LT
  – 7 with ferritin <50
  – Hepcidin – low in 9 of 11 patients and lower limit of normal in 2 of 11

• After LT
  – 11 had iron parameters performed
  – None had phlebotomy
  – Mean ferritin – 185
  – MRI – 9 had no iron overload
  – – 1 had mild iron overload
  – – 1 had high iron overload
  – Hepcidin levels normal in 10, low in 1
Liver transplantation normalizes serum hepcidin level and cures iron metabolism alteration in HFE Cys282Tyr hemochromatosis.

Bardou-Jacquet, et al. Rennes - #189 (continued)

- Liver transplantation normalizes hepcidin in long term
- LT cures phenotypic expression of HFE hemochromatosis

Prevalence of C282Y Homozygotes Without Iron Overload in Screening Studies

<table>
<thead>
<tr>
<th>Population sample</th>
<th>Country</th>
<th>n</th>
<th>Prevalence of homozygotes</th>
<th>C282Y homozygotes with a normal ferritin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electoral roll</td>
<td>New Zealand</td>
<td>1,064</td>
<td>1 in 213</td>
<td>40</td>
</tr>
<tr>
<td>Primary care</td>
<td>USA</td>
<td>1,653</td>
<td>1 in 276</td>
<td>50</td>
</tr>
<tr>
<td>Epidemiological survey</td>
<td>Australia</td>
<td>3,011</td>
<td>1 in 188</td>
<td>25</td>
</tr>
<tr>
<td>Blood donors</td>
<td>Canada</td>
<td>4,211</td>
<td>1 in 327</td>
<td>81</td>
</tr>
<tr>
<td>General public</td>
<td>USA</td>
<td>41,038</td>
<td>1 in 270</td>
<td>33</td>
</tr>
<tr>
<td>Primary care</td>
<td>North America</td>
<td>44,082</td>
<td>1 in 227</td>
<td>25</td>
</tr>
<tr>
<td>General public</td>
<td>Australia</td>
<td>29,676</td>
<td>1 in 146</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>124,636</td>
<td>1 in 240</td>
<td>41</td>
</tr>
</tbody>
</table>
**Hereditary Hemochromatosis**

**Summary**
- In 2012...
  - Most patients with hemochromatosis do not need a liver biopsy
  - Only about 60% of C282Y homozygous patients have phenotypic expression
  - About 25% of C282Y homozygous men have signs or symptoms of hemochromatosis

**Inherited Liver Diseases – WD**

**Wilson Disease - Pathophysiology**
- Gene *ATP7B* is a p-type ATPase on chromosome 13
- Impaired hepatic copper excretion
- Hepatic and extrahepatic copper deposition
Inherited Liver Diseases – WD

Wilson Disease - Genetics
• 1 in 30,000
  – Over 200 mutations in ATP7B
• His1069Glu most common
• Mutation analysis helpful in siblings

Wilson Disease - Clinical Features
• Liver disease
  – Fulminant hepatic failure
  – Chronic hepatitis
  – Cirrhosis
• Neurologic presentation
Wilson Disease – Diagnosis

- Clinical suspicion
  - Young (children, adolescents, and young adults)
  - Neurologic disease
  - Liver disease
  - Kayser-Fleischer rings
  - Low uric acid, alkaline phosphatase
  - Hemolytic anemia (Coombs negative)

Inherited Liver Diseases – WD

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Wilson Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ceruloplasmin</td>
<td>20-40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>24 hour urine copper</td>
<td>&lt;40</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Hepatic copper</td>
<td>15-50</td>
<td>250-3000</td>
</tr>
</tbody>
</table>
The Clinical, Laboratory Characteristics, Natural History and Outcome in 201 patients with Wilson Disease
Devarbhavi, et al. Bangalore, India and Doha, Qatar - #1342

• Purpose to describe and highlight WD features from single center in India to compare with patients from the West
• 201 consecutive patients from 1996-2011
• Scoring system: International group from Leilpzig

Results:

– 130 presented with liver disease
– 71 with neurological disease with or without liver disease. 27 with encephalopathy
– Consanguinity was present in 58%
– Ascites in 101
– Jaundice in 96
– Kayser Fleischer rings in 169
– Hepatomegaly in 84
Splenomegaly in 114
49 patients (24.4%) died during follow-up
2 died from HCC
13 of 15 symptomatic siblings with liver disease had same phenotype

Conclusions
- This cohort from India
  - Younger
  - Predominantly males
  - Kayser Fleischer rings > 80%
  - Consanguinity in 58%
  - HCC in 1%
Long-term outcome of a large patient cohort with Wilson disease in Austria
Beinhardt, et al., Austria - #1344

- 223 patients (2.77/100,000 inhabitants) diagnosed 1961-2011
- 165 patients were alive or their treating physician contacted to access current status as of 2011. No data available for 56 patients
- Median observation period – 14.4 years. 3,028 patient years

Long-term outcome of a large patient cohort with Wilson disease in Austria
Beinhardt, et al., Austria - #1344 (continued)

- Results:
  - 222 patients, (115 female, 107 male)
  - 133 presented with liver disease
  - 57 presented with neurologic disease
  - 22 asymptomatic
  - 22.3 years (range 2-61 years): age of symptomatic presentation
Long-term outcome of a large patient cohort with Wilson disease in Austria
Beinhardt, et al., Austria - #1344 (continued)

- 16 patients (7.2%) died during observation period
  - 12 related to WD
    - 7 hepatic decompensation
    - 3 after liver transplant
    - 1 accident
    - 1 suicide
- 28 patients (12.6%) required OLT
  - 8 fulminant, 19 ESLD, 1 worsening neurologic
  - OLT generally a few months after diagnosis
  - Survival 92% after 20 years

Conclusions:
- WD can be associated with serious, often fatal liver disease
- 12.6% require OLT
- Long-term prognosis is excellent if survive 10 years after initiation of treatment
- Early diagnosis and treatment mandatory for successful outcome
Inherited Liver Diseases – WD

Wilson Disease – Treatment
• d-penicillamine
• Trientine
• Zinc acetate
• Ammonium tetrathiomolybdate
• Liver transplantation

Wilson Disease – Family Screening
• Siblings
  – Ceruloplasmin
  – Role of genetic testing