Approach to Elevated Liver Tests

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Conflicts of Interest

- None relevant to declare
Outline

- Properties
- Patterns of liver disease
- Clinical value of different patterns & levels

Liver enzymes vs. LFTs

- Serum aminotransferase levels and alkaline phosphatase levels are liver enzymes. Their elevations indicate hepatocyte and bile duct epithelial injury.

- Albumin, bilirubin, and prothrombin time are measures of hepatic function. But these are affected by extrahepatic factors such as nutrition, hemolysis, antibiotic use.
Liver enzymes vs. LFTs

- **Special liver function tests**: GEC, ICG, MEGX, and various breath tests. Depend on metabolic function of hepatocytes and are dependent on liver blood flow.

- **Child-Pugh score** is perhaps the best indicator of liver function in patients with cirrhosis.

- **MELD score** measures more than liver function.

Aminotransferases are not specific to liver

<table>
<thead>
<tr>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (9000:1)</td>
<td>Liver (7600:1)</td>
</tr>
<tr>
<td>Muscle (5200:1)</td>
<td>Muscle (750:1)</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Red cells</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
</tr>
</tbody>
</table>
Aminotransferases: Properties

- Source of normally circulating AT is unclear.
- AST and ALT activity in liver is 7000 and 3000 times higher than in serum.
- AT are released either due to cell destruction or leaky cell membrane.
- Increased synthesis

Aminotransferases: Properties

- ALT is exclusively in cytoplasm whereas AST is both cytoplasm and mitochondrial.
- Half life of total AST 17± 5 hours; ALT 47 ± 10 hrs
- AST/ALT ratio depends on gender and age; men with higher levels than women.
Aminotransferases elevations: Non-Hepatic etiology

- Hemolysis
- Myocardial infarction
- Acute renal injury
- Infarcted bowel
- Brain injury
- Muscle injury
- Macroenzymes

Alkaline Phosphatase

- Also present in bone, placenta, intestine, and kidney.
- Alkaline phosphatase can be fractionated - bone fraction is heat labile and liver fraction is heat stable.
- Elevated GGT or 5’ nucleotidase can help hepatic vs. non-hepatic source for elevated alkaline phos.
- Alkaline phosphatase elevation is physiological in those who are less than 18 years old, or pregnant women.
Characterization of elevated liver enzymes

- Acute vs. Chronic

- Hepatocellular vs. Cholestatic vs. mixed

R-value: ALT/AP (both x ULN)
- > 5 is hepatocellular
- < 2 is cholestatic

Hepatocellular Liver Disease

**Only Acute**
- Viral Hepatitis A, E*
- Toxins
- Ischemia
- Pregnancy-related
- Herpes simplex hepatitis
- Acetaminophen

*Chronic in immunocompromised patients

**Only Chronic**
- Fatty liver
- Hemochromatosis
- A-1 antitrypsin deficiency

**Both acute & Chronic**
- Autoimmune
- Wilson's Disease
- Hepatitis B
- Budd-Chiari Syndrome
- Alcoholic liver disease
- Medications
Cholestatic Liver Disease

**Extrahepatic**
- Stones
- Cancer
- Sphincter dysfunction
- Choledochal cysts
- Trauma

**Intrahepatic**
- PBC
- Sepsis
- Drugs
- Metastases
- Granulomas
- TPN

**Both intra & extra hepatic**
- PSC
- Cholangiocarcinoma
- Radiation

Clinical value of different patterns

- In almost all liver diseases, ALT is higher than AST except in alcoholic liver disease and in advanced fibrosis.

- In alcoholic hepatitis, AST is greater than ALT
  - Alcohol increases mitochondrial AST and decreases cytoplasmic ALT.
  - ALT is also low due to pyridoxine deficiency.

- AST and ALT are significantly lower in patients with renal failure.
Clinical value of different levels

- Normal AT in patients with HCV and NAFLD may still be associated abnormal hepatic histology.
- Levels < 300 U/L in chronic HCV/HBV, NAFLD, and hemochromatosis.
- ALT > 150 or AST > 300 U/L is uncommon in alcoholic liver disease.

Clinical value of different values

- **Very high values in thousands**
  - Ischemic injury
  - Drug or toxin injury
  - Viral Hepatitis
  - Autoimmune
  - Budd-Chiari syndrome
  - CBD Stones
AT elevation in the context of other abnormalities

- Elevated bilirubin: severity of injury, hemolysis, Gilbert’s, Obstruction
- Very high levels with hemolysis: Wilson’s
- Very high levels with new onset ascites: cardiac etiology or Budd-Chiari
- Very high LDH: ischemia
- High CPK: Rhabdomyolysis
- APAP phenotype: High AT and INR but not as high bilirubin

Pattern of recovery

- Dramatically improving AT indicate ischemia or toxic injury.
- Fluctuating at high levels – congestive heart failure, surreptitious APAP intake, and arrhythmias.
Macro AST

- Normal enzymes complexed with Ig G and Ig A
- High AST, but normal ALT, alk phos, CPK
- Immunoprecipitation and electrophoresis confirm AST enzyme complex
- Can be seen in liver disease, malignancy, IBD

Keep in Mind

- Isolated asymptomatic increase in AST: Macro AST
- Jaundice or high liver tests with hemolysis: Wilson’s
- Alk phos/bili < 2: Wilson’s disease
- Acute liver disease + ascites: Budd-Chiari
- Pregnancy + ALF: HSV, HEV, AFLP
Child-Turcotte-Pugh Classification

<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
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</tbody>
</table>

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
- Class A = 5 to 6 points (least severe liver disease)
- Class B = 7 to 9 points (moderately severe liver disease)
- Class C = 10 to 15 points (most severe liver disease)

MELD Score

\[
MELD = 3.78 \times \log_e \text{ serum bilirubin (mg/dL)} + 11.20 \times \log_e \text{ INR} + 9.57 \times \log_e \text{ serum creatinine (mg/dL)} + 6.43 \text{ (constant for liver disease etiology)}
\]

NOTES:
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0.
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result).

http://depts.washington.edu/hepstudy/mgmt/mgmt/discussion.html
Take home messages

- Liver biochemistries are among the most widely ordered tests in clinical practice.
- Aminotransferases and alk phos are not liver function tests.
- Patterns of their elevation are of significant utility at the bedside.
- Child’s score is most widely used for assessing the liver function.