Liver Test Pearls-What’s New?

Pamela Kushner M.D., F.A.A.F.P.
Clinical Professor UC Irvine

Sunday June 16, 2013
8:00 AM - 9:00 AM
Faculty Disclosures

• No Conflict of Interest to disclose
1) Participants should learn about the appropriate diet prescription and management of fatty liver disease.

2) Cases will be discussed to aid in the evaluation of abnormal liver tests. Differential diagnosis will be explored.

3) The latest CDC recommendations with regard to hepatitis testing will be reviewed.
Case 1: Michael, 56-year-old male

- Comes to the office for routine checkup
- His only complaint is his inability to lose weight
- Past medical history:
  - Obesity
  - Hyperlipidemia
  - Hypertension
- Current Medications: Benazepril/Hct, simvastatin, acetaminophen and ibuprofen PRN
- Non-smoker who denies ETOH use
Drug-Related LFT Elevations

**Acetaminophen**
- 4 gm/day for 5-10 days caused elevated transaminases in >50% healthy non-drinkers
- Alcohol can potentiate hepatotoxic effects

**Statins** [common cause that may resolve spontaneously]

**Herbs**
- Black Cohosh
- Valerian
- Chaparral
- Vitamin A
- Kava Kava

**NSAIDS**

**ACE/ARB**

**ESTROGEN/TAMOXIFEN**

**PPI’s**

Almost *all Drugs* can do this.

Case 1: Michael, 56-year-old male

- Exam:
  - 142/84 mm Hg, 87 regular
  - BMI: 40
  - HEENT: no icterus
  - Lungs: clear
  - Heart: regular, no murmurs
  - Abdomen: obese, soft, nontender, no organomegaly
  - Extremities: 1+ edema, venous stasis changes, no palmar erythema
Michael

- Labs:
  - ALT: 76 U/L (normal 9-52)
  - AST: 44 U/L (normal 14-36)
  - Total bilirubin: 0.5 mg/dL (normal 0.2-1.2)
  - Total cholesterol: 209 mg/dL (normal 120-199)
  - LDL cholesterol: 112 mg/dL (normal 60-129)
  - HDL cholesterol: 31 mg/dL (normal >39)
  - Triglycerides: 282 mg/dL (normal <150)
  - Fasting glucose: 121 mg/dL (normal 70-99)
  - HgbA1c: 6.0
Physical Exam with abnormal LFTs

- Muscle wasting
- Spider nevi, palmar erythema, gynecomastia, caput medusae
- Lymphadenopathy
- Jugular venous distension
- Pleural effusion
- Terry’s Nails

http://www.ehow.com/facts_5158642_effects-cirrhosis-liver.html
Question

What is the most likely cause(s) of his problem?

1. Statin hepatotoxicity
2. Alcohol use
3. Diabetes
4. Acetaminophen use
5. NASH
6. All of the Above
Non-alcoholic Fatty Liver Disease (NAFLD)

• It is estimated that 20-30% of adult populations in developed countries have NAFLD and, although high quality data is currently lacking, the condition is clearly increasing in children also.
• Often considered a relatively benign condition, will progress to more severe stages of liver disease including NASH (non-alcoholic steatohepatitis) with or without fibrosis, cirrhosis and occasionally hepatocellular carcinoma.
• NAFLD is associated with an increased risk of developing Type 2 diabetes and treatable features of insulin resistance.
• Histological examination of liver tissue remains the only proven method to distinguish between simple steatosis and NASH, a condition far more likely to progress to cirrhosis.
• Identification of an imaging technique or non-invasive marker to achieve this distinction is therefore much sought after
• “7.3% and 8.1% is the prevalence in US in those without ETOH or hepatitis” NHANES 2002

• Non-alcoholic Steatohepatitis (NASH) diagnosis
  • Stage 1: <33% hepatocytes have fat deposited
  • Stage 2: 33%-66% hepatocytes have fat deposited
  • Stage 3: >66% hepatocytes have fat deposited
Common Liver Function Tests

- Enzymes
  - Aspartate transaminase or aminotransferase (AST, SGOT)
  - Alanine transaminase or aminotransferase (ALT, SGPT)
  - Alkaline phosphatase (ALP)
  - Gamma-glutamyl transpeptidase (GGT)
- Synthetic Function
  - Albumin
  - Prothrombin time
- Bilirubin
- Platelet count
Causes of Chronically Elevated ALT Levels

✓ Hepatic causes
  • NASH
  • Alcohol abuse
  • Infectious hepatitis
  • Autoimmune hepatitis
  • Hemochromatosis
  • Wilson’s disease
  • Alpha1-antitrypsin deficiency

✓ Nonhepatic causes
  • Celiac disease
  • Inherited disorders of muscle metabolism
  • Acquired muscle diseases
  • Strenuous exercise

Predictions of NAFLD

- Increased ALT
- Waist circumference
- BMI
- ETOH
- Male
- Mexican American, Indian
- Young
- Increased fatty acids to liver
Fat is Toxic

Excess calories
↑ Saturated fat
↑ Fructose
Lack of satiation

↑ FFA
Altered FA metabolism
↑ De novo lipogenesis

↑ Triglycerides
Hepatic steatosis

↑ FA oxidation
↑ Plasma VLDL

ROS/oxidative stress
ER stress

Insulin resistance
Hepatic and systemic

↑ TNF-α
↑ IL-6
↑ CRP
↓ Adiponectin

Lipotoxicity
Hepatocyte injury
repair/failure of repair

Inflammation
Steatohepatitis
Fibrosis

Pathway known to play significant role
Newly recognized pathway of DNL
Area of new investigation

ABC Inflammatory factor
ABC Fat
Back to Michael

• Diet/Exercise
• Pharmacology
• Monitoring LFTs
Treatment of NAFLD

- **Diet**
  - < 10 grams fat a day
  - < 100 carbs a day
  - 45-100 grams high quality animal protein a day
  - Weight loss at least 10%

- **Medications**
  - Vitamin E (α-tocopherol), 800 IUs/day in non-diabetic adults with proven NASH only
  - Pioglitazone in biopsy proven NASH
  - Statins to treat hyperlipidemia

- **Laboratory**
  - High serum ferritin and increased Iron saturation in patients with hemochromatosis gene mutations may need biopsy
  - NAFLD fibrosis score
• High risk of cardiovascular events correlate with increased NAFLD
• Prevalence of NALFD correlates with early atherosclerosis
• Fatty liver index score – calculated on BMI, WC, TG level, GGTP
  • Score of 60 or more is a marker for hepatic steatosis
• Independent of age, cholesterol, diabetes, hypertension
  • Correlation with CIMT and carotid plaque
Sylvia

• 36 year old white female presents with…
  • Nausea
  • Fatigue
  • poor appetite
  • changes in mood

• Medications
  • Birth control pills
  • 2-6 glasses of wine or beer on the weekends

• Physical Findings
  • Normal examine except for decrease of 8 pounds over the past six months

• Laboratory Findings
  • AST 88
  • ALT 44
  • GGTP 164
  • Alk phos144
  • TSH normal
  • Bilirubin normal
Transaminase Levels in Alcohol Abuse

- AST:ALT of at least 2:1
  - ETOH deficiency of pyridoxal 5-phosphate
- Gamma-glutamyltranspeptidase twice normal
- Rare for AST > 8X normal value
- Rare for ALT > 5X normal value
- Protime may be prolonged
- Decreased platelet count

ELEVATED ALKALINE PHOSPHATASE

- Cholestasis
- High fat food
- Tobacco use
- Pregnancy/growth
- CKD
Approach to predominant alkaline phosphatase elevation

- Alk phos fractionate
- 5’nucleotidase/GGTP

With increase LDH-INFILTRATIVE liver disease
Differential Diagnosis of Abnormal GGTP

- ETOH
- Diabetes
- Cholestasis (Blocked flow of bile from liver)
- CHF
- Hepatitis
- Liver Disease
- Lung Disease
- Pancreatic Disease
<table>
<thead>
<tr>
<th>GGTP Elevation</th>
<th>GGTP Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased ETOH</td>
<td>• Birth control pills</td>
</tr>
<tr>
<td>• Phenytoin</td>
<td>• Clofibrate</td>
</tr>
<tr>
<td>• Phenobarbitol</td>
<td></td>
</tr>
</tbody>
</table>
ETOH Highlights

Risky Behavior Male
• More than 4 drinks a day
• More than 14 drinks a week

Risky Behavior Female
• More than 3 drinks a day
• More than 7 drinks a week

• More than 18 million US adults have ETOH use disorder
• 40 million US adults are high risk drinkers
  • More than 5 drinks at one time can identify more than 82% of people with an alcohol abuse problem

NIAAA- National Institute of Alcohol Abuse and Alcoholism (2013)
2009 Youth Risk Survey

- 73% of students have at least one drink of ETOH within 30 days
- 24% had episodic heavy drinking within 30 days
- No single intervention has been shown to decrease ETOH intake and consequences
- Greatest intervention is when the student gets in trouble for risky behavior
- Movement in congress to change ETOH blood level to .05
John-26 year old male

- Presents to office because of abnormal LFTs on physical for new job
- No current complaints
- Medications: None
- Past Medical History: None
- History: unsafe sex, questionable drug abuse
- Normal exam
- Labs: normal lipids, glucose with ALT 104, AST 81
# The Abnormal LFT Test List

<table>
<thead>
<tr>
<th>Serum Protein Electrophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
</tr>
<tr>
<td>Anti-Smooth Muscle ABs</td>
</tr>
<tr>
<td>Liver-Kidney Microsomal ABs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIBC</td>
</tr>
<tr>
<td>HFE Genetic Testing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Ceruloplasmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour Urine Copper Excretion</td>
</tr>
</tbody>
</table>

| Serum $\alpha_1$-Antitrypsin Level |

Hepatitis C

- Over 170 million people worldwide
- 3.2 million US adults infected with only half tested who are aware of their status
  - 1/3 referred for hepatitis C care
  - Only 5-6% have been successfully treated

NEJM (May 16, 2013)
What is new in Hep C?

- Past treatment
  - Standard of care: peg interferon and ribavarin
- Now understand
  - Specific proteins involved in virus replication which can be targeted by protease (teleprevir, boceprevir) and polymerase inhibitors (sofosbuvir)
- High degree of genetic diversity
  - 6 different genotypes which differ at 35% of nucleotide sites
  - 8% sequence divergence within individual strains within a subtype
- Need to test drug candidates for genotypes
CDC recommendation for Hepatitis C
August 2012

- Test all Americans born between 1945-1965
  - 63% of newly HCV infections are in this age group
- Test for antibody test HCV
  - RNA HCV test to identify current infection
- Negative test still could mean exposure within 6 months
The Hep B Burden

- Global Burden
  - 2 billion people have had a prior Hep B infection
  - More than 400 million have chronic Hep B
  - 700,000 deaths yearly worldwide
Chronic Hep B Infection (Clearance phase)

- Insidious onset
  - Even with advanced cirrhosis or fibrosis may feel well
- Immune systems response to damage (months to years)
  - Decreased HB DNA and rise ALT
- High virus with normal ALT for a long period
- Complications
  - Liver cancer
  - Portal hypertension
  - Esophageal varices
Hep B Vaccination Recommendations for Adults with Diabetes

- ACIP (Advisory Committee on Immunization Practices) Oct 25, 2011
  - Vaccinate age 19-59 as soon as diagnosis of diabetes made (Type 1 & 2)
  - Data on risk of Hep B in adults >60 less robust
    - Assess individual risk and likelihood of adequate immune response
  - 2/3 of cases in adult diabetes, diagnosis are made before age 60 based on 2008 data
  - No serologic testing or additional vaccination for those who received a complete series
Pregnant Women and Hepatitis B

- Screen all pregnant women for HBsAg
- 5-10% of vaccination fails in babies if high viral load in mother
- First dose of HBIG within 12 hours of birth to babies of mothers who screen positive
Hep B Exposure

- Majority exposed as young children in horizontal transmission
  - Mother to child, father to child, child to child
- Unsafe sexual practices
- Unsafe medical practices
- Injection drug abuse
Does age of exposure affect risk?

- Neonate 70-90% chance of chronic infection
- 5% of adults exposed get chronic infection
- Elderly 59% get chronic infection
Major Risk Factor for Hep B is Country of Origin

- Africa, Asia, Pacific island, eastern and southern Europe, Aboriginal region
- 1:2000 general US
  - 1:10 Asian Americans
- Chronic HBV infections in Asians have a 25% lifetime risk of liver cancer or of dying from cirrhosis
Do you ever get rid of HBV?

- Immune suppression (HIV, steroids or chemo)
  - Now virus can replicate and cause damage while trying to clear
- HBV DNA can remain in liver
- At end of suppression can get reactivation so screen everybody before chemotherapy
  - May stop antiviral before you start chemo and follow 6 months after chemo to prevent withdrawal flare
HBsAg Positive

- 1st – Liver panel, CBC, creatinine, HBeAg, anti-HBe, HBV DNA
- Monitor
  - Ultrasound every 6 months in males more than 40 and females more than 50
  - African born more than 20
  - All with cirrhosis or family history of liver cancer
- Educate
  - Vaccinate household and sexual contacts
Definitions

• Immune tolerant
  • High virus, normal ALT, HBeAg +
    • Monitor ALT q3 to 6 months

• Immune active
  • High virus, increased ALT
    • Consider for therapy

• Inactive
  • Viral load less than 2000, normal ALT
Testing for Hep B

- HBsAg + > 6 months means chronic Hep B
- anti-HBs natural or vaccine induced immunity
- core antibody- exposed at some point
- HBeAg usually virus replicating at high levels
- HBV DNA- direct measure of replication overtime
Kenneth is a 24 year old graduate student from Nigeria with normal liver tests

- Viral load more than 1 million with HBeAg +
- Immune tolerant- needs treatment
  - Follow for HBeAg to be negative
- What tests?
  - PPD
  - HIV
  - CXR
  - VDRL
Causes of Hyperbilirubinemia

- **Unconjugated**
  - Gilbert’s syndrome
  - Heart Failure
  - Medications
  - Crigler-Najjar syndrome
  - Hemolysis
  - Hyperthyroidism
  - Cirrhosis
  - Wilson’s Disease

- **Conjugated**
  - Choledocholithiasis
  - Cholangiocarcinoma
  - Sclerosing Cholangitis
  - AIDS cholangiopathy
  - Pancreatitis
  - Strictures
  - Parasitic Infections
  - Viral Hepatitis
  - Alcoholic hepatitis
  - NASH

- **Other**
  - Primary Biliary Cirrhosis
  - Medications
  - Sepsis
  - Infiltrative diseases
  - Total Parenteral Nutrition
  - Pregnancy
  - End-state Liver Disease
Gilbert’s Syndrome

- Common genetic disorder
- 3-7% of the population
- Males > Females
- Mild hyperbilirubinemia (usually less than 3 mg/dL)
  - Indirect unconjugated
  - Higher with illness or fasting
- No specific therapy
Diagnosis of Gilbert's Syndrome

- Unconjugated hyperbilirubinemia on repeated testing
- Normal complete blood count, blood smear, and reticulocyte count and normal liver function tests (plasma aminotransferases and alkaline phosphatase concentrations)
- No changes in 12 to 18 months
AGA Recommendation: Mild Elevations of ALT or AST (<5 X Normal)

1. History and Physical Examination*, Discontinue hepatotoxic medications
2. Confirm abnormality if an error is suspected
3. Liver Chemistries, PT, Albumin, CBC with platelets, Hepatitis A, B and C Serologies**, Fe, TIBC, Ferritin

- Negative serology, asymptomatic patient without hepatic decompensation
  - Consider ultrasound, ANA, α-smooth muscle Ab, ceruloplasmin, α₁-antitrypsin
  - Abnormal results
  - Liver biopsy

- Positive serologic evaluation
  - Viral Hepatitis Work-up

Which of these findings suggest alcohol abuse?

1. AST:ALT ratio >2:1
2. AST > 8X normal
3. Pyridoxal 5-phosphate deficiency
4. All of the above
5. 1 and 3 only
Questions