What to do with those elevated liver enzymes

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Irving M. Rasgon MD Family Medicine Symposium
Overview

► Abnormal liver tests: a common scenario in outpatient Primary Care medicine
► LFTs part of routine chemistry panel - not advised (USPSTF) for routine care of healthy adults
► Biochemical liver tests and patterns reviewed
► Assessment of liver disease severity
► Common problems – mild transaminase elevation and non-alcoholic fatty liver disease (NAFLD)
► Ethnic and racial variation in disease prevalence
► Case examples
Goals of this Presentation

- Evaluate and understand basis for and causes of abnormal liver tests
- Estimate severity of chronic liver disease
- Evaluate mild transaminase elevations
- Understand patterns of liver disease in different ethnic and racial groups
- Refer appropriate patients for Gastroenterology evaluation
Biochemical Liver Tests

► ALT (alanine aminotransferase) = SGPT
  - Leakage from damaged hepatocytes
  - Most hepatocyte specific (cytosolic)

► AST (aspartate aminotransferase) = SGOT
  - Leakage from damaged hepatocytes
    (mitochondrial and cytosolic)
  - Also from muscle, RBCs, kidney, brain, pancreas
Biochemical Liver Tests

► AP (alkaline phosphatase)
  - Overproduction and leakage into serum
  - Produced from biliary epithelium
  - Also from bone disease, placenta, intestine
  - 5’ nucleotidase more specific to liver, can be used to confirm liver source of AP
Biochemical Liver Tests

► Bilirubin

- Conjugated and unconjugated (direct/indirect)
- Indirect reflects hemolysis or impaired metabolism of bilirubin
- Increased direct suggest hepatic and post-hepatic causes
Biochemical Liver Tests

► Prothrombin time
  - Usually expressed as INR
  - Synthesis of vitamin K dependent coagulation factors (II, VII, IX, X) occurs in hepatocytes
  - Elevation due to liver disease not corrected by vitamin K
  - Also from malnutrition, malabsorption, antibiotic use, warfarin, DIC
Biochemical Liver Tests

► Albumin

- 10 grams of albumin synthesized by liver each day
- With progressive liver dysfunction, synthetic capacity decreases
- Long serum half life and reduction from other causes make albumin a less useful test
- Consider malnutrition, volume status, renal and other vascular losses, GI tract losses
Biochemical Liver Tests

►► GGT (gamma glutamyl transpeptidase)

- Produced in liver, spleen, pancreas, lung, and other tissues
- Induced by alcohol and drugs, persists
- Not very helpful as liver test due to lack of specificity
- Normal result does not exclude alcohol use
- I avoid ordering this test
Biochemical Liver Tests

► LDH (lactate dehydrogenase)
  - Present in many tissue types
  - Lacks specificity
  - Can increase markedly in ischemic hepatitis
  - Also increases in malignant infiltration of the liver
  - I avoid ordering this test (*Little Darn Help!*).
Patterns of liver disease and LFTs

- Hepatocellular necrosis
  - Example: viral hepatitis

- Cholestasis
  - Example: primary biliary cirrhosis

- Infiltrative liver disease
  - Example: metastatic carcinoma
Patterns of liver disease and LFTs

► Hepatocellular necrosis
  - Hallmark is elevation of ALT and AST
  - May range from slight increase to >100 times normal elevations
  - AP slightly increased or normal
  - Bilirubin may be normal or very elevated, depending on severity and timing of illness
Patterns of liver disease and LFTs

► Hepatocellular necrosis
  - Severe acute elevations from relatively few causes (i.e., ALT > 15 times normal)
    - Drug/toxin induced hepatitis
    - Acute viral hepatitis
    - Ischemic hepatitis
    - Acute Budd-Chiari syndrome
Patterns of liver disease and LFTs

- Hepatocellular necrosis
  - Moderate elevations less specific (ALT 5-15 times normal)
    - Drug/toxin induced hepatitis
    - Acute and chronic viral hepatitis
    - Autoimmune hepatitis
    - Metabolic hepatitis (Wilson, alpha-1 antitrypsin)
Patterns of liver disease and LFTs

- Hepatocellular necrosis
  - Mild elevations even less specific (ALT < 5 times normal)
  - NAFLD – common!
  - Alcohol (AST > ALT)
  - Hepatitis B and C
  - Hereditary Hemochromatosis
  - Autoimmune hepatitis
  - Medications and toxins
Patterns of liver disease and LFTs

- Cholestatic liver disease
  - Hallmark is increased AP +/- bilirubin
  - Need to ensure AP is from liver and not another source
  - If AP increase is substantial (several hundred) and other LFTs normal, OR significant history of bone disease (Paget’s, metastatic cancer to bone), check 5’ nucleotidase to confirm
Patterns of liver disease and LFTs

- **Cholestatic liver disease**
  - Next step is to determine category of cholestatic disease
    - Intrahepatic (i.e., PBC)
    - Extrahepatic (i.e., choledocholithiasis)
  - Best test is RUQ ultrasound
    - Dilated bile ducts imply extrahepatic cause
    - Nondilated bile ducts imply intrahepatic cause (unless very early obstruction)
Patterns of liver disease and LFTs

► Cholestatic liver disease

- If dilated bile ducts on U/S, usual next test is abdominal CT to identify general level of obstruction, such as pancreas, CBD, hilum.
- Consultation with GI appropriate, to consider if ERCP (or MRCP prior to possible ERCP) warranted
- If ducts not dilated on U/S, CT and MRCP or ERCP unlikely to identify cause of increased AP
Patterns of liver disease and LFTs

► Dilated bile ducts and *NORMAL* LFTs

- Will occasionally encounter this scenario
- Typically in patient with pain, who undergoes U/S or CT as part of the evaluation
- Typically extrahepatic bile duct dilatation only
- Intrahepatic dilatation suggests mechanical obstructive problem
- Extrahepatic dilatation only with normal LFTs is usually not a mechanical obstructive problem responsive to ERCP / sphincterotomy / stent
Patterns of liver disease and LFTs

► Cholestasis with *NORMAL* bile duct caliber
  - Implies an intrahepatic cause of the abnormal AP +/- bilirubin
  - Serologic evaluation indicated first, reserving liver biopsy for cases where diagnosis is not clear
  - Exclusion of medication induced condition is critical, since drug hepatotoxicity is a common cause of cholestasis (50+ drugs implicated)
Cholestasis Algorithm

Elevated AP

History and Physical

Normal bili, ALT, AST

Abnormal bili, ALT, AST

5’ nucleotidase (? elevated)

RUQ U/S (? dilated ducts)

+  -  +  -

RUQ U/S  No liver disease  GI, CT, MRCP, ERCP  Intrahepatic disease

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Symposium 2007
Patterns of liver disease and LFTs

► Infiltrative liver disease

- Typically from carcinoma metastatic to liver
- Amyloidosis, Tb, sarcoidosis, fungal, lymphoma
- Liver tests may be normal, even with massive liver metastases
- If elevated, LFTs typically increase 2-3 times normal, with a tendency for a greater increase in the AP
- Imaging/biopsy key to diagnosis
Assessing severity of disease

► Pattern of LFTs determined (i.e., hepatocellular necrosis, cholestasis, or infiltrative)

► Diagnostic approach based on pattern

► How severe is the condition, and what is the prognosis?

► Need test similar to the cardiac echo, with regard to liver function (i.e., what is the physiologic “EF” of the liver!)
Assessing severity of disease

► Regardless of the cause of non-obstructive liver disease, certain tests reliably estimate liver function

► INR, bilirubin, creatinine are the best indicators

► To a lesser degree, albumin, presence of ascites, presence of encephalopathy also indicate relative liver function

► Level of transaminases and AP do not reflect degree of liver function or impairment, may even be NORMAL in end stage liver disease
Assessing severity of disease

► MELD (Model of End Stage Liver Disease) assigns a score based on INR, bilirubin, creatinine
► Range from 6-40
► Excellent predictor of mortality in absence of liver transplantation
► MELD Score = 10 \{0.957 \ln(\text{Cr}) + 0.378 \ln(\text{Tbil}) + 1.12 \ln(\text{INR}) + 0.643\}
► INR carries most weight in the formula
Assessing severity of disease

3 month mortality based on MELD score for patients awaiting liver transplantation
Assessing severity of disease

- MELD remains < 15 until significant cirrhosis present, so not particularly helpful in identifying mild-moderate fibrotic liver disease
- Increasing liver fibrosis and eventually cirrhosis leads to portal hypertension
- Portal hypertension leads to splenomegaly and decreased platelet count (< 200K)
- Low platelet count in patient with suspected chronic liver disease, even if LFTs are normal or minimally elevated, can reflect advanced fibrosis or even cirrhosis
Assessing severity of disease

- ? noninvasive measure of fibrosis/cirrhosis
- Tests using a panel of biochemical markers to estimate liver fibrosis and inflammation are commercially available
- Sleisenger and Fordtran GI and Liver Disease Textbook, 8th Ed. 2006. “FT-AT remains an experimental tool that should be used with caution until the preliminary data are confirmed in large trials”
- My opinion: not ready for prime time, but stay tuned!
Mild Transaminitis

- Frequently encountered in outpatient setting
- Defined as < 5 times normal elevation of ALT/AST (AGA Technical Review, 2002)
- Higher elevations warrant closer attention, can result in significant fibrosis sooner (months, rather than years/decades)
- Chronic hepatitis: > 6 months of elevation
Mild Transaminitis

- H/P, review alcohol & medication history
- Screen for viral hepatitis (hep A Ab, hep B sAg and sAb, hep C Ab) and Fe/TIBC/ferritin
- Ensure other liver tests are normal and no evidence for cirrhosis
- Remember, cirrhosis can be present, even with normal or near-normal ALT and AST
Mild Transaminitis

► Lifestyle modification
  - weight loss and exercise
  - stop alcohol use
  - control diabetes
  - stop potentially offending medication(s)

► Follow up for 6 months, check ALT/AST 2-3 times

► If cirrhosis or ALT > 5 times normal, expedite evaluation and/or consult with GI
Mild Transaminitis

If ALT mildly, persistently elevated for 6 months, extend evaluation (part 1)

- Ensure hepatitis B and C are negative
- Check ANA/ASMA
- Check ceruloplasmin
- Check $\alpha_1$-Antitrypsin phenotype
- Check for sprue (IgA EMA or IgA tTG)
Mild Transaminitis

► If ALT mildly, persistently elevated for 6 months, extend evaluation (part 2)
  ▪ Consider systemic illness, DM, thyroid disease
  ▪ Re-examine medications, OTCs, supplements
  ▪ Repeat liver tests including ALT, AST, Bilirubin, AP, Protime, Albumin, CBC
  ▪ RUQ U/S
  ▪ Consider GI referral, liver biopsy if no diagnosis
Mild Transaminitis Algorithm

Elevated ALT and AST < 5x NL

History and Physical

Confirm LFTs abnormal
Check for toxic meds

ALT/AST/AP, bilirubin T/D, albumin, INR, CBC
Hepatitis ABC, Fe/TIBC/ferritin

LFT > 5x

Expedite and extend liver evaluation

- Cirrhosis/- Serology

Discontinue alcohol
Exercise/weight loss
Diabetes control

Repeat LFT over 6 months

NL

Observe

+ Cirrhosis/+ Serology

GI consultation and/or directed treatment

ABN

Extend liver evaluation
Mild Transaminitis

► Now, where to go?

- Medication induced – stop drug if possible, follow closely, refer to GI if not improving
- Alcohol induced liver disease – cessation
- Sprue – small bowel biopsy, GF diet if confirmed
- Chronic viral hepatitis – refer to GI
- Autoimmune liver disease – refer to GI
- Metabolic (HHC, Wilson, etc.) – refer to GI
- Cirrhosis – refer to GI
Mild Transaminitis

Non-Alcoholic Fatty Liver Disease (NAFLD)
Mild Transaminitis

Non-Alcoholic Fatty Liver Disease (NAFLD)

- Extremely Common Diagnosis
- Surpasses alcohol as a cause of cirrhosis
- NAFLD encompasses a disease spectrum from benign steatosis to steatohepatitis with fibrosis to cirrhosis
- Most NAFLD is benign
- NAFLD does not necessarily need to see GI
Mild Transaminitis

► Non-Alcoholic Fatty Liver Disease (NAFLD)
  - Must ensure other causes of hepatitis excluded
  - Must assess severity of liver disease
  - Biopsy best method of assessment, though most of my patients do not undergo biopsy
  - If cirrhosis present, should screen annually for hepatocellular carcinoma, avoid NSAIDs/raw seafood, receive hepatitis A and B immunizations
  - Treat weight, diabetes, hypertension, hyperlipidemia
  - Arrange regular (annual) follow up, check for progressive liver disease
Patterns of liver disease in different ethnic/racial groups

Specific chronic liver diseases vary in prevalence in different E/R groups, but are not excluded based on E/R group

Hemochromatosis example: varies in prevalence (Third National Health and Nutrition Examination Survey, 1994)

<table>
<thead>
<tr>
<th>HFE Genotype</th>
<th>Non-Hispanic White (n = 2016)</th>
<th>Non-Hispanic Black (n = 1600)</th>
<th>Mexican American (n = 1555)</th>
<th>Total (N = 5171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Subjects†</td>
<td>Weighted Prevalence Estimates, % (95% CI)‡</td>
<td>No. of Subjects†</td>
<td>Weighted Prevalence Estimates, % (95% CI)‡</td>
</tr>
<tr>
<td>C282Y/C282Y</td>
<td>6</td>
<td>0.30 (0.12-0.82)</td>
<td>1</td>
<td>0.06 (0.02-0.31)</td>
</tr>
<tr>
<td>H63D/H63D</td>
<td>48</td>
<td>2.15 (1.45-3.08)</td>
<td>5</td>
<td>0.32 (0.10-0.92)</td>
</tr>
<tr>
<td>C282Y/H63D</td>
<td>47</td>
<td>2.35 (1.63-3.34)</td>
<td>1</td>
<td>0.06 (0.02-0.31)</td>
</tr>
<tr>
<td>C282Y/wild type</td>
<td>196</td>
<td>9.54 (8.03-11.30)</td>
<td>38</td>
<td>2.33 (1.52-3.44)</td>
</tr>
<tr>
<td>Wild type/wild type</td>
<td>1240</td>
<td>62.10 (59.40-64.66)</td>
<td>1465</td>
<td>91.60 (89.83-93.25)</td>
</tr>
</tbody>
</table>

†Indicates number of subjects who had positive test results for particular genotype of the total sample size for each race/ethnicity group.
‡Confidence intervals (CIs) assume a design effect of 1.5.
Patterns of liver disease in different ethnic/racial groups

- Hepatitis C prevalence varies, though not when adjusted for activities that result in high risk for infection (Hyams KJ, et al., Am J Epid 2001; 153:764-70)

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Active Duty US Military - Hepatitis C Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.4 (26/6,779)</td>
</tr>
<tr>
<td>African American</td>
<td>0.8 (15/1,989)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.6 (9/1,607)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0/336)</td>
</tr>
<tr>
<td>Native American</td>
<td>0 (0/96)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0/184)</td>
</tr>
</tbody>
</table>
Patterns of liver disease in different ethnic/racial groups

- Studies show prevalence of NAFLD in African Americans with DM less than that for Caucasian or Hispanic subjects.
- Prevalence of NAFLD: Caucasians 73% and African Americans 53% of Hispanic prevalence  
  (Browning et al., Hepatology 2004 40:1387-95)
Case Examples

- ALT 100, AST 80, AP 100, bilirubin 1.0
- Pattern: Hepatocellular
- ALT > AST
- Cause: ? Fatty liver, ? Hepatitis B or C
- Use mild transaminase elevation algorithm
Case Examples

► ALT 60, AST 120, AP 120, bilirubin 1.0, INR 0.9

► Pattern: Hepatocellular

► AST > ALT

► Cause: Think alcohol first, then other causes
Case Examples

- ALT 75, AST 65, AP 265, bilirubin 1.0
- Pattern: Cholestatic
- Check ultrasound
- No obstruction - then serologic evaluation (AMA)
- Check medications: amoxicillin/clavulanate
Case Examples

- ALT 75, AST 65, AP 265, bilirubin 4.0
- Pattern: Cholestatic
- Check ultrasound – dilated ducts
- Consult GI for possible ERCP, order CT scan
- Obstructing pancreatic cancer
Case Examples

- ALT 55, AST 50, AP 155, bilirubin 1.0
- Pattern: Nonspecific - ? infiltrative
- Check ultrasound – multiple liver masses
- Imaging guided biopsy confirms diagnosis
- Remote h/o breast cancer 5 yrs. ago
Case Examples

► Two asymptomatic patients, who has the better prognosis?

► #1: ALT 1500, AST 1350, AP 130, bilirubin 2.0, INR 1.1, Cr 1.0

► #2: ALT 21, AST 25, AP 100, bilirubin 3.5, INR 1.5, Cr 1.3

► Patient 1 has acute hepatitis, relatively preserved liver function, patient 2 has advanced cirrhosis.
Case Examples

► What does this mean?
► ALT 31, AST 27, Tbil 2.2, Dbil 0.2, AP 100
► No prior history or any symptoms
► If no hemolysis, then Gilbert’s syndrome
► Impaired bilirubin metabolism, not a liver disease
► No further evaluation needed
Case Examples

► What to do?

► Insurance exam GGT 85, patient denied

► ALT 21, AST 18, bilirubin 0.7, AP 95, GGT 80

► GGT induced by medication, alcohol (even small amounts) – very nonspecific

► Abstain from EtOH, repeat ALT/AST

► Don’t order GGT, not a valuable LFT
Summary

► Determine predominant pattern of LFTs
► Select diagnostic algorithm based on pattern
► Assess whether liver function is affected
► Consult GI for assistance based on algorithms outlined in this discussion