EVALUATION OF ABNORMAL LIVER TESTS

MIA MANABAT DO PGY6

MOA 119TH ANNUAL SPRING SCIENTIFIC CONVENTION

MAY 19, 2018
EVALUATION OF ABNORMAL LIVER TESTS

- Review of liver enzymes vs liver function tests
- Clinical assessment
- Evaluation
- Specific liver diseases
OVERVIEW

- Liver enzymes, liver chemistries, liver tests
  - AST
  - ALT
  - Alkaline phosphatase
  - (Bilirubin)
- **Markers of liver injury**, not liver function
OVERVIEW

- Liver function tests
  - Albumin
  - Prothrombin time
  - (Bilirubin)
- Markers of hepatocellular function
OVERVIEW- ALT & AST

- ALT
  - More specific marker of hepatic injury than AST
  - Present primarily in the liver

- AST
  - Present in the liver, cardiac and skeletal muscle, kidney, and brain
OVERVIEW- WHAT IS NORMAL?

• ALT
  • 29-33 IU/l for males  19-25 IU/l for females
  • There is a linear relationship between ALT and BMI
  • Normal ALT does not exclude significant liver disease
OVERVIEW- AP & BILIRUBIN

- **Alkaline phosphatase**
  - Found in **liver, bone, placenta, intestine and kidney**
  - **Liver origin** can be **confirmed by GGT or fractionation** of alkaline phosphatase
  - Elevates typically with obstruction of the bile ducts

- **Bilirubin**
  - Comes from breakdown of senescent red blood cells
  - Predominantly circulates in unconjugated form
  - Conjugated/direct bilirubin → Elevation indicates hepatocellular dysfunction or cholestasis
OVERVIEW - ALBUMIN & PT

• Albumin
  • Marker of hepatocellular function
  • Exclusively synthesized by the liver

• Prothrombin time
  • More sensitive measure of liver function
  • Measures extrinsic pathway of coagulation
    • Clotting factors 1, 2, 5, 7, 9, 10
OVERVIEW

Why is an elevated AST and ALT important?

- Prevalence of individuals with elevated ALT and AST has increased significantly in the US
- Elevated AST and ALT correlate with morbidity and mortality
  - Coronary artery disease (NHANES database)
  - Liver-related mortality (NHANES database)
  - Diabetes-related mortality (NHANES database)
  - All-cause mortality (Int Arch Occup Environ Health)
CLINICAL ASSESSMENT OF PATIENTS WITH ABNORMAL LIVER TESTS

• History- What is clinically significant alcohol consumption?

  • >21 drinks average per week in males
  
  • >14 drinks average per week in females
CLINICAL ASSESSMENT OF PATIENTS WITH ABNORMAL LIVER TESTS

• History- Risk factors for viral hepatitis?
  • Parenteral exposure- IV drug use, blood transfusion prior to 1992, tattoos, intranasal drug use
  • Travel to endemic areas
  • Family history
  • High risk sexual practices
CLINICAL ASSESSMENT OF PATIENTS WITH ABNORMAL LIVER TESTS

• History – Medications, herbal supplements, dietary supplements
  • Pain meds
  • Statins
  • Antibiotics

• Over 1000 meds and herbal supplements have been associated with drug induced liver injury
• https://livertox.nih.gov/
CLINICAL ASSESSMENT OF PATIENTS WITH ABNORMAL LIVER TESTS

• History - Statins
  • Most commonly mild asymptomatic rise in ALT early in therapy that is not clinically significant
  • Up to 3% of patients will have a persistent elevation in liver enzymes above 3x ULN
  • Severe drug induced liver injury is rare
CLINICAL ASSESSMENT OF PATIENTS WITH ABNORMAL LIVER TESTS

• History- Statins
  • In patients with mild elevations in liver enzymes, it is safe to start statins
  • U.S. FDA recommendation from February 2012: Check liver enzymes prior to initiation of statins and as clinically indicated thereafter
CLINICAL ASSESSMENT OF PATIENTS WITH ABNORMAL LIVER TESTS

• History- Statins
  • In chronic liver disease, it is reasonable to check liver enzymes 4-12 weeks after starting therapy
  • In compensated cirrhosis, some studies have shown a lower mortality rate and fewer episodes of hepatic decompensation
  • Contraindicated in patients with decompensated cirrhosis or acute liver failure
LIVER ENZYME PATTERNS

• **AST > ALT**
  - Alcohol
  - Cirrhosis of any etiology
  - Ischemic hepatitis
  - Congestive hepatopathy
  - Acute Budd-Chiari syndrome
  - Hepatic artery damage or occlusion
  - TPN
LIVER ENZYME PATTERNS

• ALT > AST
  • NAFLD
  • Viral hepatitis
  • Medications, DILI
  • Genetic causes- hemochromatosis, Wilsons, alpha-1 antitrypsin deficiency
  • Fatty liver of pregnancy, HELLP
  • Sepsis
EVALUATION OF ELEVATED LIVER ENZYMES

- Before beginning the evaluation for elevated liver tests, repeat lab test for confirmation
  - Any clarifying test should be performed
    - GGT
    - Fractionation of alkaline phosphatase
    - Fractionation of bilirubin
EVALUATION OF ELEVATED LIVER ENZYMES

- Isolated borderline (<2x ULN) or mild (2-5x ULN) elevation of AST/ALT
  - Initial evaluation:
    - Focused H&P, discontinue hepatotoxic medications, no alcohol
    - Hepatitis B & C screening
    - Hemochromatosis screening
    - Evaluate for fatty liver with RUQ abdominal ultrasound
EVALUATION OF ELEVATED LIVER ENZYMES

Borderline elevation ≤ 2x ULN

- History and physical exam
- Discontinue hepatotoxic meds
- Discontinue alcohol consumption
- Assess for risk factors for fatty liver and viral hepatitis

- CBC/platelet count, AST/ALT, Alk Phos, TB, albumin, PT/INR
- HBsAg, HbcAb, HBsAb, HCV Ab with PCR confirmation if +, iron panel, abdominal ultrasound

- If negative, consider observation for 3-6 months with repeat AST/ALT, Alk Phos, TB or ...

- If persistently elevated, continue investigation: ANA, ASMA, gamma-globulin, ceruloplasmin, alpha-1 antitrypsin phenotype and may consider additional tests based on history (e.g., celiac sprue, tick-borne disease, thyroid disease, and muscle disorders)

- If normal, further testing at discretion of clinician or refer to hepatologist for consideration of liver biopsy
EVALUATION OF ELEVATED LIVER ENZYMES

- Moderate (5-15x ULN), severe (>15x ULN), and massive (>10,000) elevations in liver enzymes
  - Require immediate evaluation for etiology and signs of acute liver failure
  - Acute hepatitis panel, CMV, EBV, HSV, ceruloplasmin, ANA, anti-smooth muscle antibody, anti-mitochondrial antibody, serum drug panel, urine toxicology, abdominal US with Doppler
  - Consider N-acetylcysteine, liver biopsy, referral to transplant center
EVALUATION OF ELEVATED LIVER ENZYMES

Moderate elevation
5-15x ULN

- History and physical exam
- Discontinue hepatotoxic meds and alcohol
- Evaluate for signs of acute liver failure

- CBC/platelet count, AST/ALT, Alk Phos, TB, albumin, PT/INR, HAV Ig M, HAV IgG, HBsAg, HBCab IgM, HBCab IgG, HBsAb, HCV Ab with PCR confirmation if +, iron panel, ceruloplasmin, ANA, SMA, and gamma-globulin
- Abdominal ultrasound

If signs of acute liver failure --> urgent liver consultation with consideration of referral to a liver transplant center

If diagnostic evaluation negative --> consideration for diagnostic liver biopsy if medically stable
EVALUATION OF ELEVATED LIVER ENZYMES

- Elevation of alkaline phosphatase
  - Isolated elevation in AP
    - Confirm with GGT
    - RUQ US, r/o hepatotoxic medications, check autoimmune antibodies (ANA, AMA, ASMA)
    - If preceding tests are negative, consider liver biopsy vs observation

- Elevated AP + AST/ALT +/- bilirubin → US & autoimmune antibodies
EVALUATION OF ELEVATED LIVER ENZYMES

- Elevation of bilirubin- unconjugated
  - H&P, AST/ALT, alkaline phosphatase
  - Review medications
  - Evaluate for hemolysis
  - If AST/ALT and alkaline phosphatase are normal, consider Gilbert’s syndrome
EVALUATION OF ELEVATED LIVER ENZYMES

- Elevated total bilirubin (predominant unconjugated)
  - History and physical exam
  - Assess liver transaminases and serum alkaline phosphatase
- Review medications
  - Evaluate for hemolysis
  - Evaluate for Gilbert's syndrome
- If persistent elevation is otherwise unexplained, may consider diagnostic testing for Gilbert's syndrome (UGT1A1 genotype) and evaluate for uncommon etiologies in Table 6
- If persistent elevation is otherwise unexplained, is symptomatic, is worsening over time, and/or associated with abnormal transaminases
  - Consider liver biopsy
EVALUATION OF ELEVATED LIVER ENZYMES

- Elevation of bilirubin- unconjugated
  - MC cause is Gilbert’s syndrome
    - Genetic defect of UDP-glucuronyltransferase
    - Affects 3-7% of US population
    - Total bilirubin is usually <3 and almost never exceeds 6
EVALUATION OF ELEVATED LIVER ENZYMES

• Elevation of bilirubin- conjugated
  • H& P, AST/ALT, alkaline phosphatase
  • Review medications
  • Evaluate for clinically overt etiologies: sepsis, TPN, cirrhosis, biliary obstruction
• RUQ US
  • If no duct dilation → ANA, ASMA, AMA
  • If persistent or worsening, consider liver biopsy
EVALUATION OF ELEVATED LIVER ENZYMES

Elevated total bilirubin (predominant conjugated)

History and physical exam
Assess liver transaminases and serum alkaline phosphatase

Review medications
Evaluate for clinically overt etiologies: sepsis, TPN, cirrhosis, and biliary obstruction
Perform right upper quadrant ultrasound

If ductal dilatation -> ERCP or MRCP
If no ductal dilatation -> check AMA, ANA, and SMA

If persistent elevation is otherwise unexplained, is symptomatic, is worsening over time, and/or associated with abnormal transaminases
-> consider liver biopsy
SPECIFIC LIVER DISEASES

• Chronic Hepatitis C-
  • Estimated 3.5 million people in U.S. have chronic infection
  • Risk factors: IV or intranasal drug use, needle stick, tattoos, blood transfusion before 1992, long-term dialysis, HIV +, children with HCV + mothers, incarceration
  • Hepatitis C antibody is 92-97% sensitive, becomes positive 6-8 weeks after exposure
  • Confirmation of infection by HCV RNA PCR assay → refer to specialist
  • *Hepatitis C screening is recommended for patients born between 1945 and 1965
SPECIFIC LIVER DISEASES

• Chronic Hepatitis C-
  • New treatments are highly effective in achieving a cure (SVR)
    • Hepatitis C antibody will be positive even after achieving cure
  • Patients should be assessed for liver fibrosis before treatment to determine the need for ongoing hepatocellular carcinoma screening
  • Vaccination against HAV and HBV
SPECIFIC LIVER DISEASES

• Chronic Hepatitis B-
  • Estimated 1.5 million people in U.S. and over 280 million people worldwide
  • Transmitted through sexual intercourse or parenteral in the U.S.
  • 3 tests to evaluate the hepatitis B status:
    • Hepatitis B surface antigen (HBsAg) → infection
    • Hepatitis B core antibody total (HBcAb) → prior exposure
    • Hepatitis B surface antibody (HBsAb) → immunity

• Refer to GI or hepatology
SPECIFIC LIVER DISEASES

- Non-alcoholic fatty liver disease (NAFLD)
  - Associated with the metabolic syndrome—DM, HTN, dyslipidemia, obesity
  - Non-alcoholic steatohepatitis (NASH) → inflammation, fibrosis, cirrhosis
  - ALT>AST rarely above 300
  - Routine screening for NAFLD in high risk groups is not advised
SPECIFIC LIVER DISEASES

• Treatment of NAFLD:
  • Lifestyle modification- diet, exercise, weight loss
  • Weight loss of 5% total body weight improves hepatic steatosis
  • Weight loss of 10% total body weight improves histopathologic findings of NASH
    • Reducing calories by 500-1000 kcal/day and moderate exercise recommended
SPECIFIC LIVER DISEASES

• Treatment of NAFLD:
  • Pioglitazone 45 mg/day have been shown to improve liver histology in patients with and without DM2
  • Vitamin E 800 IU/day has been shown to improve liver histology in patients without DM2
SPECIFIC LIVER DISEASES

- Other treatment considerations in NAFLD:
  - Due to high cardiovascular risk in patients with NAFLD, they should be treated aggressively
  - Statins are safe in patients with chronic liver disease and cirrhosis
  - Abstain from heavy alcohol use
    - Insufficient data to recommend against nonheavy/moderate consumption
TAKE HOME POINTS

• Initial evaluation for borderline to mild elevation in AST/ALT should include HBV & HCV screening, hemochromatosis screening, & RUQ US to rule out fatty liver
• Screen patients for chronic HCV in those born between 1945 and 1965
• Vaccinate chronic hepatitis B and C patients
• It is okay to treat chronic liver disease patients with statins and is recommended in patients with NAFLD/NASH
• Weight loss of 10% total body weight by maintaining a caloric deficit and regular exercise is the mainstay of treatment for NAFLD/NASH
THANK YOU
REFERENCES


