ABNORMAL LIVER TESTS, WHAT NOW?

12/9/2023

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NO CONFLICTS TO DISCLOSE

LEARNING OBJECTIVES

- Be able characterize abnormal LFTs as hepatocellular, cholestatic and/or non-hepatic etiologies
- Recognize common and uncommon causes of abnormal LFTs
- Be familiar with etiologies of abnormal LFTs in the pregnant patient
- Be able to interpret hepatitis B serology
- Recognize when to refer abnormal liver enzymes

"LFTS"

- 1-2% asymptomatic individuals
- Liver injury tests (LFTs) – AST & ALT (**hepatocellular**)/alk phos & bili (**cholestatic**)
- True LFTs – bili, albumin, protein, INR
- AST – produced by muscle as well
- Alk phos – produced by bone, liver, placenta, intestines
- Isolated hepatic alk phos elevation – think infiltrative liver disease – TB, sarcoid, lymphoma

COST OF WORKUP

Table 2. Financial Costs of Selective Serologic Tests for Assessing Hepatic Diseases

Laboratory test	Fiscal charges (U.S. dollars, 2001)	Medicaid/Medicare reimbursement (U.S. dollars, 2001)
ALT, AST, alkaline phosphatase, bilirubin	69–104	51
ALT	28–58	7
AST	28–58	18
Alkaline phosphatase	27–60	7
Bilirubin	26–104	7
Albumin	27–69	6
Prothrombin time	29–44	5
Complete blood count	46–82	8
γ-glutamyltranferase	28–65	8
5′-Nucleotidase	36–54	8
Alpha-fetoprotein	83–130	23
Hepatitis A-IgM	79–111	6–56
HBsAg	55–58	14
Hepatitis Bc-IgM	89–111	16
Hepatitis A/B profile	108	37
Hepatitis Bc-Total	49–107	17
Hepatitis Be antibody	86–111	15
Hepatitis Be Ag/Ab	32–81	26
Hepatitis B-DNA	250–300	49
Hepatitis C antibody ELISA	92–104	18
Hepatitis C-RNA qualitative	250–276	49
Hepatitis C-RNA quantitative	527–340	59
Hepatitis C genotype	578–590	70
Iron	26–57	9
Ferritin	69–120	10
Total iron-binding capacity	27–57	9
Hemochromatosis genetic analysis	263–326	N/A
Anti-nuclear antibody	58–113	17
Anti-smooth muscle antibody	73–117	8–23
Anti-liver-kidney microsomal antibody	136–205	9
Anti-mitochondrial antibody	73–170	8–23
Alpha1-antitrypsin	83–99	12
Ceruloplasmin	65–76	12
Copper, serum	77–83	16
Copper, urine	82–83	16
Abdominal ultrasonography	660	80
Liver biopsy (US-directed total cost)	>1000	43–113

NOTE. Cost data in U.S. dollars is based on the year 2001–2002 laboratory fee schedule and approximate financial reimbursement from Medicaid or Medicare at 2 university-affiliated outpatient facilities.

<3XULN AST/ALT ELEVATIONS

- **Metabolic Dysfunction-Associated Steatohepatitis** (ALT>AST) (formerly NASH or fatty liver)
- **Alcoholic liver disease** (AST:ALT 2:1)
- **Chronic viral hepatitis** B, C
- **Drug** different mechanisms of hepatotoxicity

>10XULN AST/ALT ELEVATION

- **Drug** – acetaminophen, mushrooms
- **Acute viral hepatitis** – hep A, B, E (pregnancy), CMV, EBV, HSV (pregnancy)
- **Shock** – history of syncope/hypotension and associated with multi-organ strain

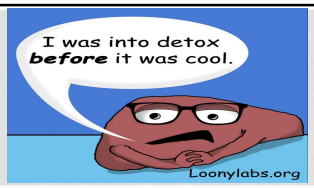
"IRON MAN"

HEMOCHROMATOSIS

- Primary – genetic, autosomal recessive (1:300)
  - Increased iron absorption
- Secondary – iron overload – thallasemic with numerous blood transfusions
- Multiple organs affected – heart, skin, arthritis (MP joints), gonads, pancreas, pituitary, thyroid
- Diagnosis
  - Screening - Iron sat >45% and elevated ferritin
  - Confirmatory – HFE gene (C282Y, H63D)

HEMOCHROMATOSIS

- Treatment
  - Primary – treat only if ferritin elevated, phlebotomy to reduce TS <50% and ferritin <50
  - Secondary - deferoxamine
- Review – Caucasian male with bronze DM -> iron sat/ferritin/HFE -> phlebotomy



"CRAZY LIVER"

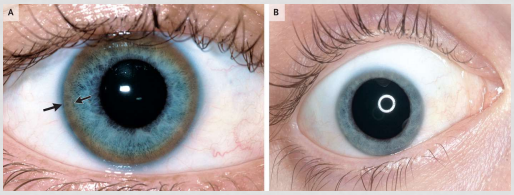
WILSON'S DISEASE

- Autosomal recessive (1:30k)
  - Decreased copper excretion
- Multiple organs – eyes (Kayser-Fleischer rings), brain
- Fulminant hepatic failure, HCC rare
- Diagnosis
  - Low ceruloplasmin (<20mg/dL)
  - Increased 24 urinary copper (>40mcg/d)
  - KF Rings
  - If not all above met then check hepatic copper concentration (>250mcg/g)

WILSON'S DISEASE

- Treatment
  - D-penicillamine many AE, give pyrodoxine with therapy
  - Trientine – fewer AE
  - Follow urine copper to monitor therapy
  - Zinc in pregnant patients

KAYSER-FLEISCHER RINGS



"MY BODY IS ATTACKING MY LIVER"

AUTOIMMUNE HEPATITIS

- Young to middle-aged women
- Associated with other autoimmune diseases
- Diagnosis
  - Many antibodies – ANA, anti-SMA, anti-SLA, anti-LKM1
  - Liver biopsy usually recommended as Ab testing low sensitivity
- Treatment
  - AST >10xULN
  - AST >5xULN + gamma-globulins >2xULN
  - Bridging fibrosis
  - Incapacitating symptoms (fatigue, arthritis)
  - Steroids -> relapsing disease, 6MP/AZA -> chronic disease

"ITCHY WOMAN"

PRIMARY BILIARY CHOLANGITIS

- Middle-aged women (1:1000)
- Fatigue, pruritis, xanthomas, hepatomegaly, osteoporosis
- Associated with SICCA, thyroid disease, scleroderma, CREST, celiac disease
- Diagnosis
  - Anti-mitochondrial antibody (95% sensitive)
  - Alk phos >1.5xULN and AST <5xULN
  - Liver biopsy? If diagnosis uncertain
  - Hyperlipidemia, osteoporosis, fat soluble vitamin deficiencies

PRIMARY BILIARY CHOLANGITIS

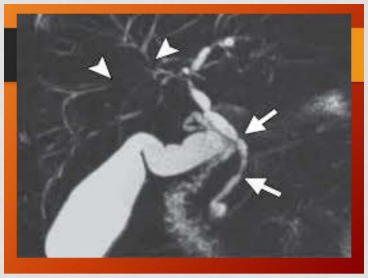
- Treatment
  - Ursodeoxycholic acid shown to improve transplant-free survival and histologic progression
  - Obeticholic acid
  - Pruritis cholestyramine
  - Watch for overlap syndromes

"COLITIC JAUNDICE"

PRIMARY SCLEROSING CHOLANGITIS

- M>F, 20-40y/a
- 60-80% with IBD but only 2-7% with IBD develop PSC
- Fatigue, pruritis, hepatosplenomegaly
- Associated with Sjogren's, celiac, RA, vitiligo, Addison's
- Diagnosis
  - MRCP if asymptomatic
  - ERCP
  - P-ANCA
- Increased malignancy risk
  - CholangioCA (1st yr), colon cancer (annual with IBD, q2-3 years without IBD), HCC, pancreatic CA

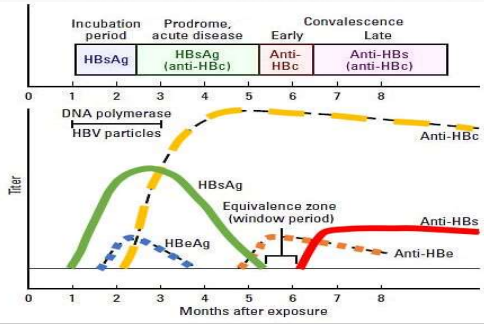
PRIMARY SCLEROSING CHOLANGITIS



HEPATITIS B

- DNA virus -> increased HCC risk
- Sexual and vertical transmission
- Hep B surface Ag -> current infection
- Hep B surface Ab -> immunity
- Hep B core Ab IgM -> recent infection or "flare"
- Hep B core Ab IgG -> remote infection
- Hep B e Ag -> high infectivity
- Hep B e Ab -> similar to core Ab IgG
- Can be reactivated with immunosuppressing agents

HEPATITIS B



HEPATITIS B

	HBsAg	Anti-HBs	Anti-HBc
Susceptible	Negative	Negative	Negative
Vaccinated	Negative	Positive	Negative
Past Infection	Negative	Positive	Positive
Acute Infection	Positive	Negative	IgM Positive
Chronic Infection	Positive	Negative	IgG Positive

HEPATITIS B

Stage	HBeAg serological status	Pattern	Indications for treatment
1. "Immune tolerant"	HBeAg positive	• Stage seen in many HBeAg-positive children and young adults, particularly among those infected at birth • High levels of HBV replication (HBV DNA levels >200 000 IU/mL) • Persistently normal ALT • Minimal histological disease	Treatment not generally indicated, but monitoring required
2. "Immune active" (HBeAg-positive chronic hepatitis)	HBeAg positive; may develop anti-HBe	• Abnormal or intermittently abnormal ALT • High or fluctuating levels of HBV replication (HBV DNA levels >2000 IU/mL) • Histological necroinflammatory activity present • HBeAg seroconversion possible, with normalization of ALT leading to "immune-control" stage	Treatment may be indicated
3. Inactive chronic hepatitis "Immune control" (previously called inactive carrier)	HBeAg negative, anti-HBe positive	• Persistently normal ALT • Low or undetectable HBV DNA (HBV DNA levels <2000 IU/mL) • Reduced risk of cirrhosis and HCC • May develop HBeAg-negative disease	Treatment not generally indicated, but monitoring required for reactivation and HCC
4. "Immune escape" (HBeAg-negative chronic hepatitis)	HBeAg negative, with or without anti-HBe positive	• HBeAg negative and anti-HBe positive • Abnormal ALT (persistent or intermittently abnormal) • Moderate-to-high levels of HBV replication (HBV DNA levels >20 000 IU/mL) • Older persons especially at risk for progressive disease (fibrosis/cirrhosis)	Treatment may be indicated
5. "Reactivation" or "acute-on-chronic hepatitis"	HBeAg positive or negative	• Can occur spontaneously or be precipitated by immunosuppression from chemo- or immunosuppressive therapy, HIV infection, or transplantation; development of antiviral resistance; or withdrawal of antiviral therapy • Abnormal ALT • Moderate to high levels of HBV replication • Seroreversion to HBeAg positivity can occur if HBeAg negative • High risk of decompensation in presence of cirrhosis	Treatment indicated

OTHERS INFECTIONS

- Hep A – food borne
- Hep D – co-infect with B
- Hep E – food borne, PREGNANCY
- EBV – common lab abnormality with mono, self limiting
- CMV – immunosuppressed, mono-like
- HSV – high ALT, normal bili, PREGNANCY
- Q-fever, leptospirosis, adenovirus

HEPATITIS C

- RNA virus
- Blood transmission
- Antibody can have false positives
- Screen all patients 18-79 (USPTF)
- Many "new" therapies available and achieve cure in >97% (8-12 weeks of therapy)

PREGNANCY RELATED LIVER DISEASES

HELLPS

- 2nd-3rd TM
- Pre-eclamptic liver disease – HTN, proteinuria, edema
- HELLPS – LDH >600, AST >70, Plts <100
- High rate of maternal/fetal complications (abruption, ARF, subcapsular hemorrhage/rupture)
- Treat – optimize BP control, prompt delivery

HYPEREMESIS GRAVIDARUM

- 1st-2nd TM
- Low level AST/ALT elevation along with nausea/vomiting
- Resolves by 20 weeks
- Not usually associated with adverse perinatal or fetal outcomes
- High recurrence rate
- Treat – B6, ginger, antiemetics, steroids, TPN

ACUTE FATTY LIVER OF PREGNANCY

- 2nd-3rd TM
- Similar to HELLPS – low platelets, 50% pre-eclamptic
- Sicker than HELPPS -> encephalopathy, hypoglycemia, coagulopathy, ascites, microvesicular steatosis
- LCHAD mutation -> deficient beta-oxidation of FA
- Treat – immediate delivery, liver transplant

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

- Pruritis in 2nd-3rd TM, Hispanics
- Exclude biliary obstruction
- Elevated bile acids
- BA >40 associated with worse fetal outcomes
- High recurrence rate, no maternal complications
- Treat – URSO, elective early delivery especially if BA >40

WHEN TO REFER

- Hepatitis – elevated transaminases
  - Obtain detailed history (EtOH, sexual and drug history, meds/herbals)
  - If <2x -> RECHECK in 3-6 months
  - If 2-5x -> RECHECK in 3 months (or less)
  - Refer if >3 fold elevation or persistently elevated
  - Varying guidelines of order of serologic workup
- Acute liver failure (ALF) – synthetic liver dysfunction (elevated INR, jaundice, encephalopathy) within 26 weeks
- Fulminant liver – ALF within 8 weeks

CAUSES SUMMARY

- Hepatocellular (AST/ALT)
  - EtOH
  - MASH
  - Meds
  - Viral
  - Iron overload
  - AIH
- Cholestatic (alk phos/bili)
  - Obstruction (stone/strictures)
  - Infiltration
  - Sepsis/CHF
  - PBC
  - PSC

BIOPSY?

- Non-Invasive Methods:
  - Fibroscan/ARFI/MR elastography (imaging)
  - Fibrospect/fibrosure (blood)
  - FIB-4, APRI (calculations)
- Biopsy reserved
  - Unclear fibrosis
  - Unclear diagnosis

ISOLATED AST ELEVATION IN UNRESPONSIVE PATIENT?

MUSCLE AST

2 PREGNANCY RELATED VIRAL HEPATITIS?

HEP E AND HSV

HEP B S AB +, HEP B S AG -, HEP B C IGM -

IMMUNIZED

HEP B S AB -, HEP B S AG +, HEP B C IGM +

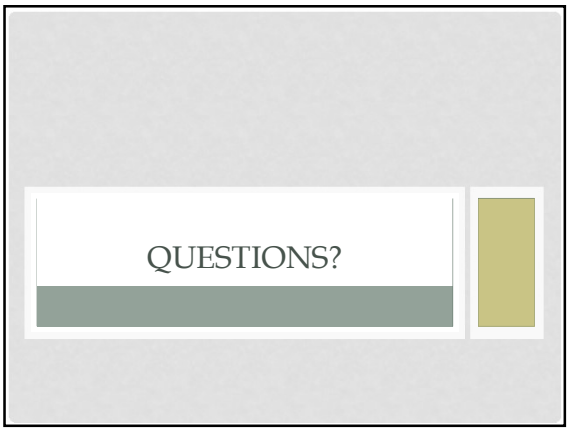
ACUTE INFECTION

HEP B S AB -, HEP B S AG -, HEP B C IGM +

WINDOW PERIOD

HEP B S AB +, HEP B S AG -, HEP B C IGG +

RESOLVED INFECTION


QUESTIONS?