Abnormal Liver Function Test

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Learning objectives

1. To understand the approach to evaluate differential diagnoses for different patterns of abnormal LFTs.
2. To learn about the type of cases that should be considered for referral to specialist clinic.

Type of Liver Function Tests

- Enzyme tests: ALT, AST, ALP, GGT
- Tests of synthetic function: Albumin, INR
- Hepatic transport capability: Bilirubin

LFT ≠ measure of liver function

- Many of the tests reflects the "health" of the liver, rather than the "function"
- May be abnormal even in patients with a healthy liver
- Normal laboratory values are defined as the mean of the distribution ± 2 SD of the "normal" population
- By definition, 5% of normal patients will have abnormalities of any given test
- Statistically, likelihood of a false positive test increases with the number of tests. 6 test = 26%

Normal Distribution

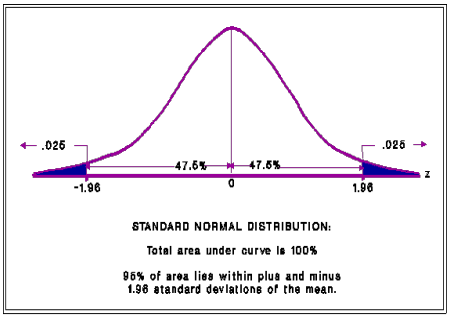

Figure 1: Areas Between and Beyond 1.96 Standard Deviations

History

- Use of or exposure to any chemical or medication (including TCM) which may be temporally related
- Duration and Time of Onset of LFT abnormalities
- Accompanying symptoms such as

1. jaundice,
2. arthralgias, myalgias, rash,
3. anorexia, weight loss,
4. abdominal pain, fever, pruritus, and
5. changes in the urine and stool

History – Clues for Aetiology

- Parenteral (body fluid) exposures including transfusions, intravenous and intranasal drug use, tattoos, and sexual activity
- Others:

1. recent travel history,
2. exposure to people with jaundice,
3. exposure to possibly contaminated foods,
4. occupational exposure to hepatotoxins, and
5. alcohol consumption

Physical Examination – Clues of Aetiology

- Dupuytren's contractures, parotid gland enlargement, and testicular atrophy are commonly seen in alcoholic and occasionally in other types of cirrhosis
- An enlarged left supraclavicular node (Virchow's node) or periumbilical nodule (Sister Mary Joseph's nodule) suggest an abdominal malignancy
- Jugular venous distension, a sign of right sided heart failure, suggests hepatic congestion

Abdominal Examination

- A grossly enlarged nodular liver or an obvious abdominal mass suggests malignancy.
- An enlarged tender liver could be viral or alcoholic hepatitis or, less often, an acutely congested liver secondary to right-sided heart failure.
- Severe right upper quadrant tenderness with respiratory arrest on inspiration (Murphy's sign) suggests cholecystitis or, occasionally, ascending cholangitis.
- Ascites in the presence of jaundice suggests either cirrhosis or malignancy with peritoneal spread.

NUHS National University Health System

NUS National University of Singapore

Overall Patterns of Abn LFT

- Pattern predominantly reflecting hepatocellular injury
  - ALT/AST > 5X ALP
- Pattern predominantly reflecting cholestasis
  - ALP > 2X ALT/AST
- Mixed pattern

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Hepatitis E

- 2009-2010 NHANES study: 6% of US population had anti HEV, suggesting prior exposure; 0.5% of those with anti HEV had IgM anti-HEV, suggesting recent infection
- 3-13% of patient with presumed DILI later found to have HEV
- Chronic hepatitis E reported in LT patients; responds to immunosuppression withdrawal and ribavirin

Dilah et al Hepatology 2014;
Kuniholm MH et al HD 2009
Leise M, et al Mayo Clin Proc 2014

Table 2. Clinical Manifestations of Hepatitis E

Hepatic manifestations
Icteric hepatitis (similar to other forms of viral hepatitis)
Severe hepatitis leading to fulminant hepatic failure
Anicteric hepatitis (biochemical abnormalities but no jaundice)
Inapparent or asymptomatic infection
Acute-on-chronic liver disease
Rare extrahepatic manifestations
Acute pancreatitis
Hematological manifestations: thrombocytopenia, hemolysis
Autoimmune phenomena: Membranous glomerulonephritis, Henoch-Schonlein purpura
Neurological syndromes
Guillian-Barre syndrome
Meningoencephalitis
Pseudotumor cerebri
Cranial nerve palsies
Bilateral pyramidal syndrome
Peripheral neuropathy

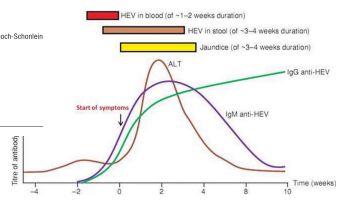
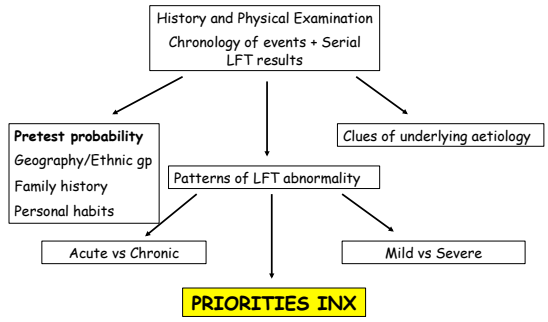


Fig. 3. Events during HEV infection. The course of a typical HEV infection is shown pre- and postsymptoms that include jaundice and liver damage (measured as ALT rise). The duration of viremia (HEV in blood), virus shedding (HEV in stool), and anti-HEV antibody responses are shown.

Aggarwal and Jameel, Hepatology 2011

Diagnostic Approach



Common Patterns

1. Mild chronic elevation in serum aminotransferases
2. Isolated hyperbilirubinaemia
3. Isolated elevation of ALP and/or GGT
4. Liver diseases in Pregnancy
5. Critically-ill hospital patients

Mild Chronic Elevation in Serum Aminotransferases

- **Chronic** (defined as six months or greater), **mild** elevation (defined as less than 250 U/L) of one or both of the aminotransferases

Step one —identify medications and supplements that can cause elevation of the serum aminotransferases, to assess for alcohol use, and to test for viral hepatitis B and C, and fatty liver.

Mild Chronic Elevation in Serum Aminotransferases

Step two — The next set of tests is aimed at identifying rarer liver conditions including autoimmune, Wilson's disease, hemachromatosis, alpa1 antitrypsin deficiency, non-hepatic causes of elevated aminotransferases, which include principally muscle disorders and thyroid disease. Rarely occult celiac disease and adrenal insufficiency.

Step three — A liver biopsy is often considered in patients in whom all of the above testing has been unyielding. However, in some settings, the best course may be observation.

- *Modified from AGA technical review: Evaluation of liver chemistry tests*

Increased AST:ALT ratio

- In a study of hundreds of patients who had liver biopsy confirmed liver disorders, more than 90% of the patients whose AST to ALT ratio ≥ 2 had alcoholic liver disease (96% if >3X) Cohen, JA, Kaplan, MM. The SGOT/SGPT ratio — an indicator of alcoholic liver disease. Dig Dis Sci 1979; 24:835.
- May also be occasionally occur in patients with nonalcoholic steatohepatitis, hepatitis C, ischemic hepatitis

Isolated Hyperbilirubinemia

- **Unconjugated hyperbilirubinemia**

1. Bilirubin overproduction (such as hemolysis and ineffective erythropoiesis)
2. Impaired hepatic uptake/conjugation of bilirubin (eg Gilbert's disease, Crigler-Najjar syndrome, and drugs)

- **Conjugated hyperbilirubinemia**

1. Cholestatic disorder (with ALP/GGT elevation)
2. Rare inherited conditions: Dubin-Johnson syndrome and Rotor syndrome

Evaluation of Hemolysis as Cause of Unconjugated Hyperbilirubinemia

General tests	Specific tests
Blood smear	Hemoglobin electrophoresis
Erythrocyte indices and reticulocyte count	G-6-PD assay
Haptoglobin level	Coombs' test
Lactic dehydrogenase level	Osmotic fragility test
Bone marrow examination	Ham's test

Isolated Elevation of ALP and/or GGT

- **ALP sources**: liver (immunolocalized to the microvilli of the bile canaliculus), bone, placenta (pregnancy), intestinal (bld gp O, B, post-prandial, familial); age related (adolescent)

- *Causes include*

1. Bile duct obstruction by stone, sludge, stricture
2. PBC, PSC
3. Metastasis to the liver
4. Drugs such as androgenic steroids and phenytoin
5. Infiltrative diseases include sarcoidosis, other granulomatous diseases

Isolated Elevation of ALP and/or GGT

- **Step 1** – Determine the source: GGT, electrophoretic separation, heat or urea denaturation
- **Step 2** – If hepatic origin, U/S HBS KIV ERCP/MRCP and AMA KIV liver biopsy
- If ALP< 50 % above normal, all of the other liver tests are normal, and asymptomatic, consider observation

Am J Gastroenterol 2000; 95:3206

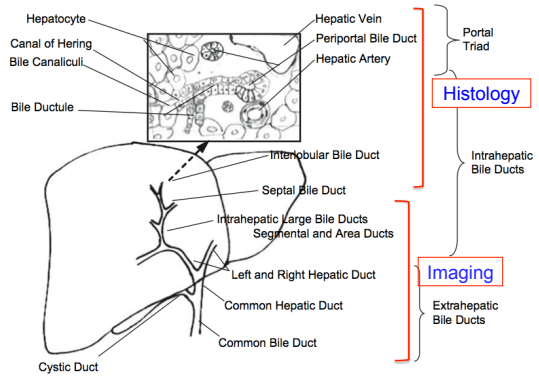


Fig. 1. Normal biliary anatomy.

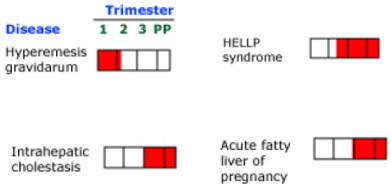
Gamma glutamyl transpeptidase (GGT)

- Found in hepatocytes and biliary epithelial cells
- Lack of specificity. Elevated in pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, diabetes, and alcoholism, use of phenytoin and barbiturates
- Elevated GGT with otherwise normal liver tests should NOT lead to an exhaustive work-up for liver disease

Etiology of Jaundice in Pregnancy

First and second trimesters	Third trimester
Gallstones	Cholestasis of pregnancy
Viral hepatitis	Preeclampsia
Alcoholic liver disease	HELLP syndrome
Cholestasis of pregnancy	Acute fatty liver
Hyperemesis gravidarum	Gallstones
	Viral hepatitis

"*Use of gestational age of the pregnancy is the best guide to the differential diagnosis of liver disease in the pregnant woman*" – ACG Guideline



Presentation

Hyperemesis gravidarum	intractable nausea and vomiting, with dehydration and ketosis
Intrahepatic cholestasis	modest pruritus to intractable itching associated with jaundice
HELLP syndrome	abdominal pain, pre-eclampsia *hemolysis, elevated liver tests, low platelets*
Acute fatty liver of pregnancy	asymptomatic to fulminant liver failure

Etiology of Jaundice in the Critically Ill Patient

Hepatocellular pattern	Cholestatic pattern	High Bilirubin	Mixed pattern
Liver ischemia	Parenteral nutrition	Transfusion	Multiple coincidental factors
		Haematoma	
		Hemolysis	
Congestive heart failure	Sepsis	Sepsis	Sepsis
Drugs	Drugs	Drugs	Drugs

*Attention should be directed to **surgical procedures** and the **intraoperative course**, episodes of **hypotension, sepsis, medications, transfusions**, evidence of **heart failure**, and **feeding route**

Abnormal LFT – Ask yourself…

1. What is the pattern?
    1. Hepatocellular injury
    2. Cholestatic
    3. Mixed
    4. Isolated enzyme abnormality

Abnormal LFT – Ask yourself…

2. Is it a liver, or something else?
    1. Part of systemic disorder?
    2. Enzyme from non-liver tissue?

Abnormal LFT – Ask yourself…

3. If hepatocellular, what are the possible causes? What other tests are needed?
    1. History
    2. Specific viral markers
    3. Specific autoimmune, metabolic markers
    4. Imaging

Abnormal LFT – Ask yourself…

4. If cholestatic, at what level? What cause?
    1. Ultrasound, CT, MRI/MRCP, EUS, ERCP
    2. Liver biopsy
    3. Immunological markers – anti-mitochondria Ab, ANCA

Abnormal LFT – Ask yourself…

5. How severe? Is there liver decompensation? Is it liver failure?
    1. History – trajectory of disease progression
    2. Physical exam – HE, ascites, jaundice
    3. Other tests – INR, creatinine, acidosis, ammonia

Refer if…

1. Life-threatening conditions e.g. ALF, cholangitis, tumor rupture…
2. Decompensation – clinical jaundice, encephalopathy, ascites, bleed
3. Diagnosis which requires specialized therapies e.g. antiviral agents, high dose steroids…
4. Suspected malignancy e.g. high AFP, liver mass…
5. If tests required are not available in your clinic

Patterns of Abnormality

Predominant hepatocellular injury	Predominant Cholestatic	Mixed	Isolated HyperBIL	Isolated Elevated ALP/GGT
•HBsAg, Anti-HBs Ab	•Intrahepatic AMA/ERCP		•Unconjugated	Source of ALP
•Anti-HCV	vs		Confirm hemolysis	U/S HBS
•HAV IgM	•Extrahepatic		Cause of hemolysis	AMA
•U/S HBS	U/S HBS		•Conjugated	ERCP/MRCP
•Caeruloplasmin, 24hr u. Cu	CT Abdomen		Cholestasis	Liver biopsy
•ANA, Anti-Sm	ERCP vs MRCP		Inherited disease	

Thank you for your attention!

Questions?

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