Dr.narges Ansari

MD

Pediatric Gastroenterologist and Hepatologist

Approach to

Liver Function Tests

The most common tests used in clinical practice include:

- Serum aminotransferases
- Bilirubin
- Alkaline phosphatase
- Albumin
- Prothrombin time

These tests are often referred to as "**liver function tests**“

Abnormal test in 1-4% of asymptomatic population

Normal tests do not exclude diseases

Application

- Noninvasive method to screen for the presence of liver disease
- Measure the efficacy of treatments for liver disease
- Monitor the progression of a disease
- Reflect the severity of liver disease

- Normal test reference values are usually arbitrarily defined as those occurring within 2 SD from the mean
- As a result, 5% of healthy individuals who have a single screening test will have an abnormal result (2.5% will have an abnormally high result)

+ & - 2 standard deviations(2 x 2.5%)

- Age
- Gender (↑ male)
- Blood group
- Post prandial state
- pregnancy

- Note: abnormal tests not always reflective of liver disease

- Elevation of serum aminotransferases indicates hepatocellular injury
- Elevation of the serum total bilirubin and alkaline phosphatase indicates cholestasis

Elevation of serum enzyme tests can be grouped into two categories:

- Enzymes that reflect generalized damage to hepatocytes
- Enzymes that reflect cholestasis

Table 1. Common Serum Liver Chemistry Tests

Liver chemistry test	Clinical implication of abnormality
Alanine aminotransferase	Hepatocellular damage
Aspartate aminotransferase	Hepatocellular damage
Bilirubin	Cholestasis, impaired conjugation, or biliary obstruction
Alkaline phosphatase	Cholestasis, infiltrative disease, or biliary obstruction
Prothrombin time	Synthetic function
Albumin	Synthetic function
□- Glutamyltransferase	Cholestasis or biliary obstruction
Bile acids	Cholestasis or biliary obstruction
5/-Nucleotidase	Cholestasis or biliary obstruction
Lactate dehydrogenase	Hepatocellular damage, not specific for hepatic disease

Serum Aminotransferases

- The serum aminotransferases (formerly called transaminases) are sensitive indicators of liver cell injury
- Alanine aminotransferase (ALT, serum glutamic-pyruvic transaminase [SGPT])
- Aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase [SGOT])

- The serum ALT and AST concentrations are normally less than 30 to 40 IU/L
- ALT levels are normally higher in men, and vary directly with BMI and to a lesser degree with serum lipid levels
- Consumption of coffee and especially caffeine may lower serum ALT levels by mechanisms that are incompletely understood

- ALT is present in highest concentration in the liver
- AST is found, in decreasing order of concentration, in the liver, cardiac muscle, skeletal muscle, kidneys, brain, the pancreas, lungs, leukocytes, and erythrocytes and is less specific than ALT for liver disease

- Clearance of the serum aminotransferases is similar to that of other proteins, involving catabolism by the reticuloendothelial system; AST is cleared more rapidly than ALT
- The half-life in the circulation is about 47 hours for ALT, about 17 hours for total AST and, on average, 87 hours for mitochondrial AST
- The major site of AST clearance is the hepatic sinusoidal cell

- The serum aminotransferases may be falsely elevated or decreased under certain circumstances
- Falsely low serum AST (but not ALT) is seen in patients with renal failure
- Serum AST activity increases significantly after hemodialysis
- Subnormal values of serum ALT have been described in patients with Crohn's disease, the reason for which is unclear

- Elevations up to eight times the upper limit of normal are nonspecific
- The highest elevations occur in disorders associated with extensive hepatocellular injury, such as acute viral hepatitis, shock liver (ischemic hepatitis), and acute drug- or toxin-induced liver injury

- The extent of liver cell necrosis correlates poorly with the magnitude of serum aminotransferase elevation
- The absolute elevation in serum aminotransferases is of little prognostic value since the liver can recover from most forms of acute injury
- Rapid decrease in plasma AST and ALT levels, together with a rise in the plasma bilirubin concentration and prolongation of the prothrombin time, is indicative of a poor prognosis in patients with acute fulminant hepatitis

History

- A complete medical history is the single most important part of the evaluation of the patient with elevated LFTs
- The use of or exposure to any chemical or medication (prescription and OTC medications and herbal therapies)
- The duration of LFT abnormalities
- The presence of any accompanying symptoms such as jaundice, arthralgias, myalgias, rash, anorexia, weight loss, abdominal pain, fever, pruritus, and ect.

- The patient should also be carefully questioned about possible parenteral exposures including transfusions, intravenous and intranasal drug use, tattoos, and sexual activity
- Other important questions include recent travel history, exposure to people with jaundice, exposure to possibly contaminated foods, occupational exposure to hepatotoxins, and alcohol consumption

- The patient should also be carefully questioned about possible parenteral exposures including transfusions, intravenous and intranasal drug use, tattoos, and sexual activity
- Other important questions include recent travel history, exposure to people with jaundice, exposure to possibly contaminated foods, occupational exposure to hepatotoxins, and alcohol consumption

Medications and drugs

Acetaminophen
Alpha-methyldopa
Amoxicillin-clavulanic acid
Amiodarone
Carbamazepine
Dantrolene
Disulfiram
Etretinate
Fluconazole
Glyburide
Halothane
Heparin
HMG-Co a reductase inhibitors
Isoniazid
Ketoconazole
Labetolol
Nicotinic acid
Nitrofurantion
Nonsteroidal anti-inflammatory drugs
Phenylbutazone
Phenytoin
Prophylthiouricil
Propylthiouricil
Sulfonamides
Trazadone
Troglidazone
Valproic acid
Zafirlukast

Herbs/ alternative Medications
- Chaparral leaf
- Ephedar
- Gentian
- Germander
- Jin Bu Huan
- Senna, Kavakava
- Scutellaria (skullcap)
- Shark cartilage
- Vitamin A

Illicit drugs
- Anabolic steroids
- Cocaine
- Ecstasy (MDMA)
- Phencyclidine (PCP)

Toxins
- Carbon tetrachloride
- Chloroform
- Dimethlfomamide
- Hydrazine
- Hydrochlorofluorocarbons
- 2-Nitropropane
- Trichloroethylene
- Toluene

Physical Examination

- The P/E should focus upon findings suggesting the presence of liver disease
- Growth failure suggest longstanding diseases
- Stigmata of chronic liver disease include spider nevi, palmar erythema, gynecomastia, caput medusae
- Jugular venous distension, a sign of right sided heart failure, suggests hepatic congestion

Laboratory Testing

A critical step in guiding the evaluation is determining the overall pattern of the abnormal LFTs, which can be broadly divided into two categories:

- Patterns predominantly reflecting hepatocellular injury
- Patterns predominantly reflecting cholestasis

diseases	AP	SGOT	SGPT	LDH
Acute hepatocellular injury	2+	4 +	4 +	±
Alchoholic hepatitis	+	2 +	+	±
Infectious mono	یا + 2 +	3 +	+3	+ 2 یا+
Cholestatic jaundice	3 +	2 +	+2	±
Carcinoma	3+	2 +	+2	+2 3+ یا
1⁰ biliary cirrhosis	4+3 یا	2 +	+2	+
Alchoholic fatty liver	+	+	±	±
Cirrhosis	+	+	+	+
Chronic hepatitis ± cirrhosis	+	3 +	+2	+

+	2-4 times
2+	4-10 times
3+	10-20 times
+4	>20 times

- The laboratory evaluation of patients with chronic, mild elevation of one or both of the aminotransferases is best achieved in a stepwise fashion to eliminate unnecessary testing
  - Chronic: defined as six months or greater
  - Mild: defined approximately as less than four times the upper limit of normal

Step One

- The first step should be to identify medications and supplements that can cause elevation of the serum aminotransferases, and to test for viral hepatitis, and fatty liver
- Almost any medication can cause an elevation of liver enzymes (NSAIDs, antibiotics, statins, anti-epileptic drugs, and anti-tuberculous drugs)
- Herbal preparations and illicit drug use

- Features suggesting drug toxicity include:
  - lack of illness prior to ingesting the drug
  - clinical illness or biochemical abnormalities developing after beginning the drug
  - improvement after the drug is withdrawn
- If the identified medication is essential to the patient's well-being and no suitable substitute is available, a liver biopsy is occasionally necessary to determine the nature and severity of liver injury

Step Two

- The next set of tests should look for non-hepatic causes of elevated aminotransferases, which include principally muscle disorders and thyroid disease
- Much less common causes are occult celiac disease and adrenal insufficiency

Muscle Disorders

- Elevated serum aminotransferases may be caused by disorders that affect organs other than the liver, most commonly striated muscle
- Serum AST and ALT may both be elevated with muscle injury
- Their ratio depends in part upon when they are assessed relative to the muscle injury
- Immediately after muscle injury, the AST/ALT ratio is generally greater than three, but approaches one within a few days because of a faster decline in the serum AST

- Conditions that can cause this include subclinical inborn errors of muscle metabolism, acquired muscle disorders (polymyositis), seizures, and heavy exercise (running)
- If striated muscle is the source of increased aminotransferases, serum levels of creatine kinase, LDH, and aldolase will be elevated at least to the same degree
- The creatine kinase or aldolase levels should be determined if other more common hepatic conditions have been ruled out

Thyroid Disorders

- Thyroid disorders can produce elevated aminotransferases by unclear mechanisms
- An assay for TSH is a reasonable screening test for hypothyroidism while a full set of thyroid function tests should be checked if hyperthyroidism is suspected

Celiac Disease

- Several reports have described elevated serum aminotransferases in patients with undiagnosed celiac disease
- The cause is uncertain
- The ALT usually slightly greater than AST
- Serum aminotransferases returned to normal following a gluten free diet
- The diagnosis of celiac disease is suggested by appropriate antibody screening with serum anti tTG-IgA antibodies

Adrenal Insufficiency

- Aminotransferase elevation (1.5 to 3 times the upper limit of normal) has been described in patients with adrenal insufficiency (due to Addison's disease or secondary causes), including those without obvious clinical features of the disorder
- Aminotransferases normalize within one week following appropriate treatment

Step Three

Autoimmune hepatitis

- A useful screening test for AIH is the serum protein electrophoresis
- > 80% of patients with AIH will have hypergammaglobulinemia A greater than twofold polyclonal elevation of the immunoglobulins supports the diagnosis
- Additional tests commonly ordered include ANA, ASMA, and anti-LKMA
- Elevated gamma globulins and high titer autoantibodies should prompt a liver biopsy to confirm the diagnosis of AIH

Wilson Disease

- The initial screening test for Wilson disease is a serum ceruloplasmin
- Patients should also be examined by an ophthalmologist for KF rings
- If the ceruloplasmin is normal and KF rings are absent, but there is still a suspicion of Wilson disease, the next test is a 24-hour urine collection for quantitative copper excretion
- The diagnosis is usually confirmed by a liver biopsy for quantitative copper
-

Step Four

- A liver biopsy is often considered in patients in whom all of the above testing has been unyielding
- In some settings, the best course may be observation
- **Whom to observe:** The ALT and AST are less than twofold elevated and no chronic liver condition has been identified by the above noninvasive testing

Whom to Biopsy

- The ALT and AST are persistently greater than twofold elevated
- While it remains unlikely that the biopsy will provide a diagnosis or lead to changes in management, it is often reassuring to the patient and clinician to know that there is no serious disorder

↑AST and LDH: hemolysis- myopathy

↑ AST and CPK: myopathy- CVA- MI

Rapid ↓ enzymes with
Increase in bilirubin and prolongation of PT ? poor outcome

Isolated Hyperbilirubinemia

- The initial step is to fractionate the bilirubin to determine whether the hyperbilirubinemia is predominantly conjugated or unconjugated
- An increase in unconjugated bilirubin in serum results from either overproduction, impairment of uptake, or impaired conjugation of bilirubin
- An increase in conjugated bilirubin is due to decreased excretion into the bile ductules or backward leakage of the pigment

Unconjugated Hyperbilirubinemia

- Disorders associated with bilirubin overproduction:
  - Hemolysis
  - Ineffective erythropoiesis
- Disorders related to impaired hepatic uptake/conjugation of bilirubin:
  - Gilbert's disease
  - Crigler-Najjar syndrome
  - Effects of certain drugs

Conjugated Hyperbilirubinemia

- Elevated conjugated hyperbilirubinemia is found in two rare inherited conditions: **Dubin-Johnson syndrome** and **Rotor syndrome**
- Patients with both conditions present with asymptomatic jaundice typically in the second decade of life
- The defect in Dubin-Johnson syndrome is altered excretion of bilirubin into the bile ducts, while Rotor syndrome appears to be due to defective hepatic storage of bilirubin

Isolated Elevation of the Alkaline Phosphatase

- Serum alkaline phosphatase is derived predominantly from the liver and bones, although other sources may contribute to serum levels in some settings
- Alkaline phosphatase levels also vary with age
- Infants and toddlers occasionally display transient marked elevations of alkaline phosphatase in the absence of detectable bone or liver disease

- Alkaline phosphatase levels are generally higher in children and adolescents because of physiological osteoblastic activity
- Levels may be up to three times higher than in healthy adults
- Individuals with blood types O and B can have elevated serum alkaline phosphatase after eating a fatty meal due to an influx of intestinal alkaline phosphatase
- There are also reports of a benign familial occurrence of elevated serum alkaline phosphatase due to intestinal alkaline phosphatase

Determining the Source of the Alkaline Phosphatase

- The first step in the evaluation of an elevated alkaline phosphatase is to identify its source
- Although electrophoretic separation is the most sensitive and specific way to do this, these tests are not widely available
- If gel electrophoresis is not available, either a 5'-nucleotidase or GGT should be obtained

- These tests are usually elevated in parallel with the alkaline phosphatase in liver disorders but are not increased in bone disorders
- An elevated serum alkaline phosphatase with a normal 5'-nucleotidase or GGT should prompt an evaluation for bone diseases
- Chronic cholestatic or infiltrative liver diseases should be considered in patients in whom the alkaline phosphatase is determined to be of liver origin and persists over time

Initial Testing for Alkaline Phosphatase of Hepatic Origin

- The most common causes include partial bile duct obstruction, primary sclerosing cholangitis, and certain drugs such as androgenic steroids and phenytoin
- Initial testing should include a right upper quadrant ultrasound
- In patients with biliary dilatation or choledocholithiasis cholangiography (either MRCP or ERCP) should be done to identify the cause of obstruction

Gamma Glutamyl Transpeptidase

- In normal full-term neonates, serum GGT activity is six to seven times the upper limit of the adult reference range; levels decline and reach adult levels by 5 to 7 months of age
- GGT is sensitive for detecting hepatobiliary disease, but its usefulness is limited by its lack of specificity
- Elevated levels in a wide variety of clinical conditions, including pancreatic disease, renal failure, diabetes, and alcoholism
- High serum GGT values are also found in patients taking medications such as phenytoin and barbiturates

Gamma Glutamyl Transpeptidase

Major sources of GGT

Liver (hepatocytes and epithelium of small bile ductules)
Pancreas, Renal tubules, spleen, brain, breast, small intestine.

- Inducible by phenobarbital, phenytoin, warfarin but not valproic acid

- جهت تشخیص ضایعات کبدی ناشی از سدیم والپروات تست خوبی است چون تا GGT نمی شود واقعی نداده باشد باعث بالا رفتن Hepatotoxicity زمانی که.

cont

Lactate Dehydrogenase

- This test is not as sensitive as the serum aminotransferases in liver disease and has poor diagnostic specificity, even when isoenzyme analysis is used
- It is more useful as a marker of myocardial infarction and hemolysis

Urobilinogen

- Conjugated bilirubin Intestinal Bacteria Urobilinogen
- 20% reabsorbed (Enterohepatic circulation)
- Small amount in urine
- Hepatic dysfunction→ more urobilinogen in urine
- Biliary obstruction → not present in urine
- Antibiotics or diarrhea→ ↓urobilinogen production
- Between 12 and 16 pm → ↑in urine


Thank
You