



INTERPRETATION OF LIVER FUNCTION TESTS PART 1

Compiled by Dr S. Mahabeer

3rd Quarter 2016

The liver function test (LFT) is a commonly requested test, and abnormal results are often detected in asymptomatic patients. The components of the test profile are total (T Bili) and direct or unconjugated bilirubin (D Bili), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (Alk phos), gamma-glutamyltransferase (GGT), total protein (TP) and albumin. The term liver function test is really a misnomer as most of these do not directly measure the function of the liver. They reflect different aspects of the health of the liver, i.e. hepatocyte integrity (AST and ALT), synthesis and secretion of bile (bilirubin and ALP) and protein synthesis (albumin).

Elevations in liver enzymes can be physiological, e.g. increased Alk phos in adolescents or pregnant women. In asymptomatic patients who have minor liver enzyme elevations (i.e. less than twice the upper limit of normal), the LFT should be repeated on a follow-up sample to confirm the result.

LFT abnormalities can often be grouped into one of three patterns:

- **Hepatocellular pattern:** There is a disproportionate elevation in the aminotransferases (AST and ALT) compared with Alk phos; bilirubin may be elevated.
- **Cholestatic pattern:** There is a disproportionate elevation in the alkaline phosphatase compared with AST and ALT; bilirubin may be elevated.
- **Isolated hyperbilirubinaemia:** Patients have an elevated bilirubin level with normal AST, ALT and Alk phos levels.

The aminotransferases (AST and ALT)

AST and ALT are sensitive indicators of liver cell injury, and are helpful in recognising hepatocellular diseases such as hepatitis. Symptoms associated with hepatocyte damage include jaundice, right upper quadrant pain, jaundice, pale stools and dark urine. AST can be found in the liver, cardiac and skeletal muscle, kidneys, brain, pancreas, lungs, erythrocytes and leucocytes, and therefore lacks specificity. Since the highest concentration of ALT is found in the liver, it is a more specific indicator of liver cell injury. Aminotransferase levels also vary according to sex and age, therefore this information should be included on the request form to obtain appropriate reference ranges on the final report.

When there are significant elevations of these enzymes, a detailed history and comprehensive physical examination needs to be performed to identify possible causes.

1. **Acute liver failure:** This is characterised by marked elevations in AST and ALT (more than 15 times the upper limit of normal), hepatic encephalopathy and a prolonged prothrombin time.
2. **Marked elevations without acute liver failure:** Consider drug ingestion (e.g. paracetamol overdose), acute viral hepatitis (including hepatitis A, B, C, E, HSV, VZV, CMV and EBV), exacerbation of chronic viral hepatitis, alcoholic hepatitis, auto-immune hepatitis, malignant infiltration, HELLP syndrome (in pregnant women), sepsis, toxin exposure, etc.
3. **Mild to moderate elevation:** Mild to moderate AST and ALT elevations (less than 15 times the upper limit of normal) are often seen with chronic liver disease and can be caused by a variety of conditions (Table 1).

Table 1. Causes of chronically elevated aminotransferase levels

Hepatic causes
Alcohol abuse
Medications
Chronic hepatitis B or C
Auto-immune hepatitis
Steatosis
Haemochromatosis
Wilson's disease
Alpha-1 antitrypsin deficiency
Non-hepatic causes
Strenuous exercise
Acquired muscle diseases
Inherited disorders of muscle metabolism
Coeliac disease

Alcohol abuse

It is often difficult for physicians to identify patients who consume excess alcohol, as they may conceal information about consumption. Early intervention can modify behaviour patterns associated with alcohol dependency, and reverse or stop further organ damage. The laboratory diagnosis is supported by the finding of an AST to ALT ratio of at least 2:1. If the GGT level is also elevated (i.e. at least twice the upper limit of normal), this strongly suggests the diagnosis of alcohol abuse. However, the lack of specificity of an elevated GGT level precludes its use as a single test to diagnose alcohol abuse. An increased mean corpuscular volume (MCV) is often seen on the full blood count in chronic heavy drinkers, and correlates with both the amount and the frequency of alcohol ingestion. Carbohydrate deficient transferrin (CDT) is useful in distinguishing chronic heavy drinkers from light social drinkers. The combination of CDT and GGT has a higher diagnostic sensitivity, and a stronger correlation with the amount of alcohol consumed than either marker alone.

Medication

Drug-induced liver injury can occur following the use of both prescription and over the counter medications, herbal preparations and recreational drugs. A careful history is vitally important to identify an ingested substance as the cause of elevated aminotransferase levels. Common prescription medications include non-steroidal anti-inflammatory drugs, antibiotics (e.g. penicillin and nitrofurantoin), anti-tuberculosis drugs (e.g. isoniazid), statins (e.g. simvastatin), sulphonylureas and anti-epileptic drugs (e.g. phenytoin and carbamazepine). Recreational drugs and substances of abuse that may cause elevations in liver enzyme levels include anabolic steroids, cocaine, ecstasy, phencyclidine (PCP or angel dust), glues and solvents.

Chronic Hepatitis (Hepatitis B and C)

Initial serological tests for hepatitis B infection should include hepatitis B surface antigen (HBsAg), core antibodies (anti-HBc) and surface antibodies (HBsAb). The presence of HBsAg indicates infection with hepatitis B virus, and its presence for more than 6 months indicates chronic infection. The most important risk factor for chronic hepatitis B infection is chronologic age at time of infection. For example, more than 90% of perinatally-infected infants will fail to clear the infection naturally and become chronically infected, compared to less than 5% of immunocompetent adults.

Serological testing for hepatitis C antibody is used as a screening test for hepatitis C infection. All positive hepatitis C antibody results should be confirmed with an HCV PCR as the serology test has excellent sensitivity, but lower specificity and positive predictive value (especially in low prevalence areas and in the absence of known risk factors for hepatitis C). Acute hepatitis C infection should be diagnosed with an HCV PCR, as it takes 6 – 8 weeks after exposure for antibodies to develop.

Auto-immune hepatitis

Auto-immune hepatitis can occur in children and adults of all ages, but is often diagnosed in women in their 40s or 50s. A thorough clinical history, and a high level of suspicion is required, as patients are often asymptomatic, and the disease may have an insidious onset and fluctuating course. Initial symptoms may be non-specific, e.g. fatigue, weight loss and skin rashes. If there are elevated aminotransferases and clinical findings suggestive of an auto-immune disorder, serum protein electrophoresis, anti-nuclear antibody and an auto-immune hepatitis profile should be requested. More than 80% of patients with auto-immune hepatitis have a polyclonal gammopathy on serum protein electrophoresis.

Hepatic steatosis

The only evidence of this condition may be a mild elevation in aminotransferase levels (usually less than 4 times the upper limit of normal), and an AST:ALT ratio < 1:1. Fatty infiltration of the liver can be identified by ultrasonography or CT scan. Non-alcoholic fatty liver disease is usually seen in patients with central obesity, type 2 diabetes mellitus, metabolic syndrome and dyslipidaemia.

Haemochromatosis

Cost-effective screening for this autosomal recessive hereditary disorder starts with an iron profile. A transferrin saturation value (obtained by dividing the serum iron level by the total iron binding capacity) of more than 45% is suggestive of haemochromatosis. A serum ferritin level > 400 ng/mL in men, and > 300 ng/mL in women further supports the diagnosis. Measurement of serum ferritin provides less specific information as it is an acute phase reactant, and will thus increase in a number of inflammatory conditions. Genetic testing is now available to identify the mutation in the HFE gene that causes the majority of cases.

Wilson's disease

This autosomal recessive genetic disorder of biliary copper excretion must be considered in younger patients (< 40 years of age) with unexplained, persistently elevated aminotransferase levels, especially if the patient also has neurologic or psychiatric abnormalities. The initial screening test is the measurement of caeruloplasmin levels, which are decreased in about 85% of patients with Wilson's disease. This is usually followed by a 24 hour urine collection for quantitative measurement of copper excretion.

Alpha-1 antitrypsin deficiency

This condition is an uncommon cause of chronic liver disease in adults, but should be considered in younger patients with emphysema. There is a decreased or absent peak in the alpha globulin region on serum protein electrophoresis. Alpha-1 antitrypsin levels may also be measured directly. Genetic testing is advised in these patients.

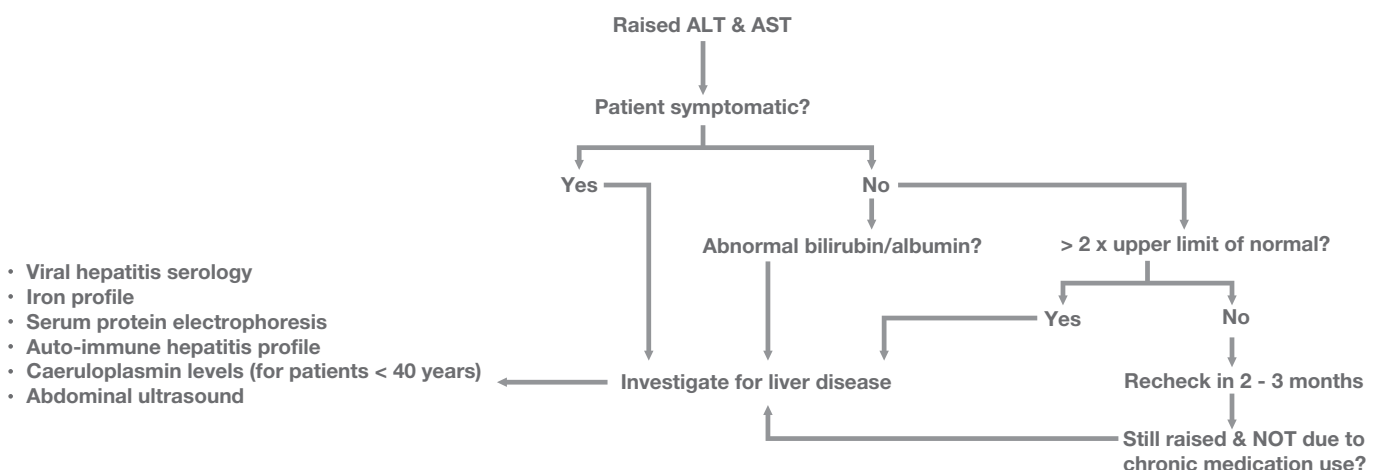
Non-hepatic causes

When more common causes of elevated aminotransferase levels have been excluded, then consider requesting tissue transglutaminase and anti-endomysium antibodies, which may reveal a diagnosis of coeliac disease. Thyroid disorders, adrenal insufficiency and malignant infiltration may also cause raised aminotransferase levels.

Increased AST levels alone may be caused by strenuous exercise or muscular disorders e.g. polymyositis. Serum levels of creatinine kinase and aldolase are usually increased, often significantly, in muscle disorders.

Figure 1 suggests an algorithm for the evaluation of raised aminotransferases.

Figure 1. Suggested algorithm for the evaluation of raised aminotransferases. (Adapted from 3.)



References:

1. Pratt DS and Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. NEJM 2000; 342(17): 1266 – 1271.
2. Friedman LS. Approach to the patient with abnormal liver biochemical and function tests. In UpToDate. Chopra S (Editor).
3. Limdi JK and Hyde GM. Evaluation of abnormal liver function tests. Postgrad Med J 2003; 79: 307 – 312.
4. Sharpe PC. Biochemical detection and monitoring of alcohol abuse and abstinence. Ann Clin Biochem 2001; 38: 652 – 664.
5. Larson AM. Drug induced liver injury. In UpToDate. Lindor KD (Editor).
6. Friedman LS. Liver biochemical tests that detect injury to hepatocytes. In UpToDate. Chopra S (Editor).