Abnormal Liver Function Tests

Most tests measure hepatocellular damage rather than function, so they are rather misnamed. True liver function tests (LFTs) are those that measure synthesis of proteins made by the liver (albumin, clotting factors) or the liver's capacity to metabolise drugs[1].

LFTs are not specific to specific systems or disease processes, yet abnormalities may indicate significant or serious disease. Interpreting abnormal LFTs and trying to diagnose any underlying liver disease is a common scenario in Primary Care. Single abnormalities in LFTs are difficult to localise and diagnose[2]. However, the pattern of abnormalities tests helps determine origin of the issue. This usually means dividing the clinical picture into non-hepatic, hepatocellular and cholestatic patterns of abnormality. When this is then combined with a clinical history, medication and drug history and the presence of any current or recent symptoms, it is usually possible to develop a differential diagnosis[1, 3].

Abnormal LFTs do not necessarily indicate any underlying abnormality of function. Traditionally, 'normal' values are defined as being within ± 2 standard deviations of the mean (of a normally distributed range), meaning that just over 95% of a healthy population will fall within the 'normal range', but 2.5% of a normal population will be normal outliers lying above it, and a further 2.5% will be normal outliers lying below it. However, as liver disease is frequently asymptomatic, this argument should not be used as an excuse for inadequate investigation. Abnormal LFTs are often inadequately investigated - which may miss an early opportunity of identifying and treating chronic liver disease[4].

Common liver investigations

LFTs are often included as a baseline investigation for a large number of different presentations. They usually consist of:

**Bilirubin**
- Bilirubin is derived from the breakdown of haem in the red blood cells within the reticuloendothelial system.
- This unconjugated bilirubin then binds albumin and is taken up by the liver.
- There it is conjugated, rendering it water-soluble and allowing it to be excreted into the urine.
- Total serum bilirubin is usually measured; however, levels of the unconjugated and conjugated portions can be determined by measures of the fractions of indirect bilirubin and direct bilirubin respectively[1].

**Albumin**
- This is a sensitive marker of hepatic function, although not useful in the acute stages as it has a long half-life (20 days). Low levels may be a function of nutritional problems, protein loss through renal disease, failure of protein synthesis through extensive loss of functioning liver tissue and some inflammatory conditions where the liver switches to making other proteins.

**Total protein**
- This measures the total of albumin and globulins, the two main proteins. It is usually normal in liver disease, as globulin levels tend to increase as albumin levels fall. High values are seen in chronic active hepatitis and alcoholic hepatitis. They are also in conditions which increase the globulin fraction significantly, most commonly in those with overactivity of the immune system, such as acute infection, chronic inflammatory disease and multiple myeloma.

**Transferrases**
- Usually either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is measured - most laboratories do not routinely provide both:
  - These proteins both indicate leakage from damaged cells due to inflammation or cell death.
  - They normally reside inside cells (in cytoplasm), so raised levels usually represent hepatocellular damage. ALT is more specific to the liver, as AST is also found in cardiac and skeletal muscle and red blood cells.
  - Creatinine kinase (CK) levels can help determine the source of raised transferrases: raised CK will confirm muscle damage and raised troponins will localise this to the heart.
  - Liver disease is more likely when the values of AST and ALT are higher, ALT rising more than AST in acute liver damage. Very high levels (>1000 IU/L) suggest drug-induced hepatitis (eg, paracetamol), acute viral hepatitis (A or B), ischaemic, or (rarely) autoimmune hepatitis.
  - The ratio of AST to ALT can give some extra clues as to the cause: in chronic liver disease ALT >AST, once cirrhosis is established AST >ALT. The level of the ratio of AST:ALT can also be helpful: >2 suggests alcoholic liver disease, and a ratio of <1.0 suggests non-alcoholic liver disease[5].
  - Serum levels below the quoted range do not signify disease; they signify only that the patient's result is in the lowest 2.5% of the population. When damage occurs, levels rise within hours and remain elevated for a few days.

**Gamma-glutamyltransferase (GGT)**
- All liver diseases may show altered GGT serum levels.
- GGT levels may be 2-3 times greater than the upper reference value in more than 50% of the patients with non-alcoholic fatty liver disease and above the upper reference value in about 30% of patients with chronic hepatitis C infection.
Raised GGT in patients with chronic liver disease is associated with bile duct damage and fibrosis. The lack of specificity but high sensitivity for liver disease makes GGT useful for identifying causes of altered ALP levels.\(^2\)

**Alkaline phosphatase (ALP)**
- ALP comes mainly from the cells lining bile ducts but is also in bone.
- Marked elevation is typical of cholestasis (often with elevated GGT) or bone disorders (usually normal GGT). If the GGT concentration is normal, a high ALP result suggests bone disease.
- Isoenzyme analysis may help identify source.
- ALP is physiologically increased when there is increased bone turnover (eg, adolescence) and is elevated in the third trimester of pregnancy (produced by the placenta).

When basic LFTs are abnormal, ensure a full history and examination are performed:

### History and examination of a patient with abnormal LFTs

**Full history**
- Recent travel.
- Transfusions.
- Drugs, including paracetamol overdose and herbal remedies.
- Tattoos.
- Unprotected sexual intercourse.
- Drug history (including herbal remedies).
- Alcohol.
- Occupation.
- Diabetes mellitus, obesity, hyperlipidaemia (all associated with fatty liver disease)\(^6\).
- Family history.

**Full examination**
- Look especially for:
  - Stigmata of chronic liver disease - eg, icteric skin, sclera and mucous membranes, palmar erythema, bruising, spider naevi, gynaecomastia.
  - Hepatomegaly - establish whether the liver feel smooth or hard, regular or irregular. Note whether it is tender.
  - Splenomegaly.
  - Ascites.
  - Obesity (associated with a fatty liver).
  - Any clues to the underlying cause - eg, lymphadenopathy.
  - Features suggestive of hepatic encephalopathy.
Further tests to consider

- Check the other transaminase - in order to ensure you have both ALT and AST results. The ratio of AST to ALT may be useful for distinguishing fatty liver due to alcoholic and non-alcoholic aetiologies.
- Prothrombin time (INR) - sensitive marker of hepatic synthetic function.
- Viral serology - eg, hepatitis A (HAV), hepatitis B (HBV) and hepatitis C (HCV), cytomegalovirus (CMV), Epstein-Barr virus and possibly HIV.
- Autoantibody screen - eg, antimitochondrial antibody, anti-smooth muscle antibody and antinuclear antibody.
- Immunoglobulins (if not available, raised immunoglobulins may be suggested by a raised globulin fraction (total protein minus albumin)).
- Serum ferritin and transferrin saturation.
- Alpha-fetoprotein (AFP).
- Copper/ceruloplasmin.
- Alpha-1 antitrypsin (A1AT).
- Imaging: ultrasound is non-invasive and helpful to detect structural abnormalities.

Interpretation of abnormal liver function tests

Consider local epidemiology
For example, about 60% of cases of elevated AST in Wales are attributable to ischaemic or toxic liver injury, whereas about 60% of cases of hepatitis in the Far East are due to oro-faecally transmissible hepatitis viruses. The incidence of primary biliary cirrhosis ranges from 1.9-2.2 per 100,000 in Australia to 0.34-0.42 per 100,000 in Asia[1].

Consider patient characteristics
Consider the age of the patient, comorbid conditions and ingestion of medications. For example, Wilson's disease is more likely to present in younger patients than in elderly ones.

Consider drug toxicity (in all cases)
Almost any medication can alter liver enzymes, including over-the-counter and herbal remedies. Take a careful and complete medication history.

Common patterns of abnormal LFTs[1]
There are some common patterns to abnormality which may point the clinician towards a predominantly hepatocellular or predominantly cholestatic picture (or a non-hepatic picture). The full analysis should involve looking at:

- Predominant pattern of enzyme alteration (hepatocellular vs cholestatic).
- Magnitude of enzyme alteration in the case of aminotransferases (<5 times, 5-10 times or >10 times the upper reference limit, or mild, moderate or marked).
- Rate of change over time.
- Pattern of the course of alteration (eg, mild fluctuation vs progressive increase).

Rise in bilirubin alone
Bilirubin is the product of haemoglobin breakdown. In the liver insoluble unconjugated bilirubin is conjugated to glucuronic acid by UDP-glucuronyltransferase and excreted into bile.

Determine whether this is unconjugated hyperbilirubinaemia or conjugated hyperbilirubinaemia. This can be determined by measuring the direct bilirubin component of the total bilirubin (>50% confirms the presence of conjugated hyperbilirubinaemia):

Unconjugated

- Unconjugated bilirubin may increase because of increased bilirubin production or decreased hepatic uptake or conjugation or both.
- In adults, the most common conditions associated with unconjugated are haemolysis and Gilbert's syndrome.
- Gilbert's syndrome is determined by genetic defects in UDP-glucuronyltransferase that affect about 5% of the population.
- Unconjugated bilirubin usually does not exceed 68 μmol/L, and other LFTs and liver ultrasound are normal.
- Other less common causes of unconjugated hyperbilirubinaemia include reabsorption of large haematomas and ineffective erythropoiesis:
  - Haemolysis - check reticulocyte count, blood film, haptoglobins, lactate dehydrogenase (LDH) and may need direct Coombs' test. Liaise with haematologist.
  - Drugs.
  - Gilbert's syndrome.
  - Crigler-Najjar syndrome.

Conjugated[2]

- In healthy people, conjugated bilirubin is virtually absent from serum because of the rapid process of bile secretion.
- Levels increase when the liver has lost at least half of its excretory capacity:
  - Increased conjugated bilirubin is usually a sign of liver disease.
  - It may be present in cholestatic drug reactions and in autoimmune cholestatic diseases.
Biliary obstruction can cause conjugated hyperbilirubinaemia. Severity depends upon degree and duration of obstruction and the functional reserve of the liver.

Other causes include Dubin-Johnson Syndrome and Rotor's Syndrome

Raised serum aminotransferase levels

Hepatitic picture: rise in AST and ALT greater than ALP and GGT

- Alcohol - fatty infiltration and acute alcoholic hepatitis (usually associated with markedly deranged liver function).
- Cirrhosis of any cause - alcohol being one of the most common.
- Medications - eg, phenytoin, carbamazepine, isoniazid, statins, methotrexate, paracetamol overdose, amiodarone (transaminases may be >1000 IU/L).
- Chronic HBV and HCV.
- Acute viral hepatitis - eg, HAV, HBV and HCV and cytomegalovirus (CMV) infection.
- Autoimmune hepatitis.
- Neoplasms - primary or secondaries.
- Haemochromatosis.
- Metabolic - glycogen storage disorders, Wilson's disease.
- Ischaemic liver injury - eg, severe hypotension,
- Fatty liver disease (mild elevation in transaminases <100 IU/L).
- Non-hepatic causes: coeliac disease, haemolysis and hyperthyroidism.

Mild increases in aminotransferases

- A minimal or mild increase in aminotransferase level is the most common biochemical alteration encountered in everyday clinical practice.
- Non-alcoholic fatty liver disease is the most common cause of mild alteration of liver enzyme levels in the western world.[1]
- Chronic HCV infection is also characterised by aminotransferase levels fluctuating around the upper limit of normal.
- The picture includes mildly raised aminotransferase levels, and GGT levels up to three times the upper reference value in the absence of ethanol consumption.
- All patients with mild increases in aminotransferase levels should be questioned about risk factors for HBV or HCV infection. Testing for HCV antibodies and hepatitis B surface antigens is advisable.
- Haemochromatosis is a relatively common autosomal recessive condition that may cause an hepatitic picture.
- Mild elevation in aminotransferase levels in female patients with co-existing autoimmune disorders suggests autoimmune hepatitis.
- Up to 10% of patients with inexplicably raised transaminases actually have coeliac disease. Minimal or mild alteration of aminotransferase levels may be the only visible tip of the 'coeliac iceberg'[7].
Marked increases in aminotransferases

- Patients with acute viral or ischaemic or toxic liver injury reach the highest aminotransferase levels.
- There is a broad overlap in aminotransferase values between patients with acute alcoholic hepatitis and autoimmune hepatitis as well as between patients with chronic hepatitis and liver cirrhosis.
- Very high aminotransferase levels (>75 times upper reference limit) indicate ischaemic or toxic liver injury in >90% of cases, and are less commonly seen in acute viral hepatitis.
- In about 80% of patients with ischaemic injury, bilirubin level is <34 μmol/L. LDH, a marker of ischaemic damage, may reach high concentrations.
- Ischaemic and hypoxic acute liver damage are more likely in patients with other clinical conditions such as sepsis or hypotension.
- In acute viral hepatitis, aminotransferase levels usually peak before jaundice appears and have a more gradual decrease afterwards.
- Jaundice is seen in around 70% of cases of HAV, 33-50% of cases of acute HBV infection and 20-33% of cases of acute HCV infection.
- The full alphabet of viral hepatitis (A, B, C, D and E) may cause a large increase in aminotransferase levels. The increase associated with HCV infection tends to be less than for HAV or HBV infection.
- Patients with acute viral hepatitis may lack history of exposure to risk factors and may have nonspecific symptoms.
- HAV is most commonly symptomatic (70-80%), followed by HBV (30-50%) and then HCV (20%).
- After the most common causes of acute liver injury have been excluded, consideration should be given to minor hepatitis viruses (eg, Epstein-Barr virus, CMV) and to autoimmune, extrahepatic and congenital causes.
- Autoimmune hepatitis may present with a mild increase in aminotransferase level.

<table>
<thead>
<tr>
<th>Cause</th>
<th>ALT/AST (x normal)</th>
<th>Bilirubin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic</td>
<td>&gt;10 to &gt;50</td>
<td>&lt;5</td>
<td>AST&gt;ALT, levels fall rapidly after peak</td>
</tr>
<tr>
<td>Toxic</td>
<td>&gt;10</td>
<td>&lt;5</td>
<td>AST&gt;ALT, history suggests toxic injury</td>
</tr>
<tr>
<td>Acute viral</td>
<td>&gt;5</td>
<td>5-10</td>
<td>ALT/AST slowly decrease after peak</td>
</tr>
<tr>
<td>Acute obstructive</td>
<td>5-10</td>
<td>&gt;5</td>
<td>ALT/AST rise precedes bilirubin rise</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>5-10</td>
<td>&gt;5</td>
<td>AST/ALT&gt;2</td>
</tr>
</tbody>
</table>

Obstructive/cholestatic: rise in ALP and GGT exceeds rise in aminotransferases

Liver injury with a cholestatic pattern is less common. The level of GGT is often measured as an additional aid.

Cholestasis

This may be intrahepatic or extrahepatic (bilirubin will also be raised).

Intrahepatic

- Primary biliary cirrhosis.
- Drugs.

Extrahepatic

- Gallstone in common bile duct.
- Neoplasm of head of pancreas.
- Drug-induced liver injury may also present with a cholestatic pattern. Commonly used drugs such as antihypertensives (eg, angiotensin-converting enzyme (ACE) inhibitors) or hormones (eg, oestrogen) may cause cholestasis, as may erythromycin, tricyclic antidepressants, flucloxacillin, the oral contraceptive pill and anabolic steroids.
- Cardiac failure (cholestasis improves with treatment).
- Primary biliary cirrhosis - more common in women, the first sign is a rise in ALP.
- Primary sclerosing cholangitis.
- Neoplasm - primary (rarely) and secondaries.
- Familial (benign).

Isolated rises in liver enzymes; GGT

- GGT is an enzyme present in hepatocytes and biliary epithelial cells, renal tubules, and the pancreas and intestine.
- Elevated GGT levels are seen in a variety of non-hepatic diseases, including COPD and renal failure, and for some weeks after acute myocardial infarction.
- Isolated rise is most commonly due to alcohol abuse, or enzyme-inducing drugs. In these patients, GGT serum levels can be markedly altered (>10 times the upper reference value), whereas ALP levels may be normal or only slightly altered. The rise is not related to the amount of alcohol intake: many heavy alcohol users may have normal GGT.
• Stopping alcohol for four weeks should rectify the abnormality.

Isolated rise in ALP
• ALP is an enzyme that transports metabolites across cell membranes.
• Liver and bone diseases are the most common causes of pathological elevation of ALP levels, but ALP may also originate from placenta, kidneys, gut or white blood cells.
• ALP rises in the third trimester of pregnancy (comes from the placenta - a normal finding).
• In the case of isolated rise in ALP, consider other sources - eg, bone or kidney.
• Varying degrees of ALP alteration in patients with inflammatory bowel disease (most commonly ulcerative colitis) suggest the presence of primary sclerosing cholangitis (about 70% are associated with inflammatory bowel disease)[2].
• Raised ALP in middle-aged women with a history of itching and autoimmune disease raises the suspicion of primary biliary cirrhosis.
• In patients with primary sclerosing cholangitis or primary biliary cirrhosis, serum bilirubin levels have prognostic significance.
• Isolated abnormal ALP levels may also be a sign of metastatic cancer of the liver, lymphoma or infiltrative diseases such as sarcoidosis.
• In the elderly consider:
  • Fractures.
  • Paget's disease of bone.
  • Osteomalacia.
  • Bony metastases (ALP is not usually raised in myeloma or osteoporosis without fracture).

Occasionally, the liver enzymes (eg, ALP, GGT, AST or ALT) may all be similarly elevated making it difficult to determine whether it is a cholestatic or hepatic picture.

Albumin and prothrombin time[2]
• Hepatic synthesis of albumin tends to decrease in end-stage liver disease.
• An increase in prothrombin time usually results from decreased clotting factors I, II, V, VII and X, which are produced in the liver but prothrombin time may also be prolonged by warfarin treatment, and deficiency in vitamin K.
• Low albumin levels are also nonspecific for liver disease since albumin serum levels may decrease in patients with nephrotic syndrome, malabsorption or protein-losing enteropathy, or malnutrition.
• Hypoalbuminaemia or prolonged prothrombin time without alteration in other LFTs are unlikely to be of hepatic origin.
• However, when it is certain that the cause is liver disease, serum albumin levels and prothrombin time are useful for monitoring liver synthetic activity.
• The half-life of albumin in circulation is long (about 20 days), and the half-life of blood clotting factors is quite short (about one day).
• Therefore, albumin levels have prognostic meaning in chronic liver conditions whilst clotting factors may compensate, leading to preservation of prothrombin time.
• Prothrombin time is more likely to be deranged rapidly in conditions of acute liver failure when it may be a sensitive prognostic indicator of acute liver failure.

Management plan
Any liver abnormalities with evidence of hepatic dysfunction (eg, low albumin, raised INR) should be referred for specialist investigation and follow-up[8].

Slightly abnormal LFT rise
• If there is a slightly abnormal rise in LFTs (ie less than twice upper limit of normal):
  • Repeat LFTs. Consider viral serology and ultrasound.
  • If tests remain abnormal and no cause is found on investigation in a well patient, consider secondary care referral for further investigation. Remember, a number of disorders of the liver may cause fluctuating mild abnormalities.
  • If you suspect the cause to be alcohol-related then inform the patient and ask them to abstain, and repeat the tests.
  • Other lifestyle changes may help - eg, good diabetes mellitus control and weight loss.
  • If remaining abnormal for longer than six months then consider referral to a specialist.
  • If the patient is unwell despite slightly abnormal LFTs then he or she may need to be referred more urgently.

Very abnormal LFTs
• If there are very abnormal LFTs (ie more than twice the upper limit of abnormal):
  • Organise further blood tests and imaging.
  • Refer to outpatients - if you suspect the cause may be malignancy then an urgent cancer referral should be made[8].

Hospital admission
Consider urgent referral for hospital admission if a patient is unwell. For example, he or she has:

• Severe jaundice.
• Severe ascites.
• Encephalopathy.
• Sepsis.
• Haematemesis of coffee ground vomiting.
Evidence of disordered clotting.
Rapid deterioration.

Further reading & references

- Guidelines on the management of abnormal liver blood tests; Gut (Nov 2017)
- Heathcote J; Abnormal liver function found after an unplanned consultation: case outcome. BMJ. 2004 Aug 28;329(7464):500; discussion 500-1.

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