Clinical and biochemical assessment of symptomatic and asymptomatic liver disease

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Abstract

Asymptomatic abnormal liver function tests (LFTs) are common, affecting 8% of the population. They are mainly caused by alcoholic liver disease and non-alcoholic fatty liver disease, whereas jaundice is most commonly caused by extrahepatic biliary obstruction, followed by alcoholic liver disease and acute liver injury from drugs or viruses. A careful history helps to exclude non-hepatic causes of abnormal LFTs, as well as indicating a potential hepatic cause. Cirrhosis can present with ascites or jaundice, the latter being common in alcoholic liver disease as a result of added injury from alcoholic hepatitis. Investigations in asymptomatic patients are intended to identify those with progressive liver disease, recognizing that cirrhosis can be clinically silent in the early stages. Concurrent clinical hepatomegaly, thrombocytopenia and splenomegaly warrant further investigation to exclude cirrhosis. An ultrasound scan and a serological chronic liver disease screen remain the standard investigations. Liver biopsy still has an important role to play in diagnosis, but other non-invasive markers of liver fibrosis can differentiate mild fibrosis from cirrhosis. Hepatitis E is becoming more common in the developed world as a cause of endemic acute hepatitis. Systemic immunoglobulin G4 disease/autoimmune pancreatitis should be considered in the differential diagnosis of cholestatic biochemistry.

Keywords Alkaline phosphatase; ascites; hepatitis B; hepatitis C; jaundice; liver function tests; MRCP; non-alcoholic fatty liver disease

Key points

- An abnormal liver blood test can be caused by systemic disease and not by primary liver disease
- Hepatitis E is endemic in the UK and is an important cause of acute viral hepatitis that mimics hepatitis A
- Non-alcoholic fatty liver disease (NAFLD) is a common cause of elevated alanine aminotransferase in the presence of a negative chronic liver disease screen and metabolic risk factors such as type 2 diabetes
- There is now more widespread use of non-invasive markers of liver fibrosis for identifying patients with NAFLD and chronic viral hepatitis who have a favourable prognosis
- Liver enzyme concentrations can be normal in cirrhosis, which should be suspected in the presence of a low platelet count and splenomegaly

Frequency

Abnormal liver function tests (LFTs) are found in 8% of the general population, the prevalence being highest in individuals with a history of heavy alcohol intake or with risk factors for the metabolic syndrome who are at risk of developing non-alcoholic fatty liver disease (NAFLD).[1] The aim of investigation is to identify cirrhosis, which in the early stages is usually asymptomatic, and liver disease that will progress if untreated. Undiagnosed cirrhosis and progressive liver disease eventually present with symptoms including jaundice, liver failure or complications of portal hypertension, such as ascites, variceal bleeding and hepatic encephalopathy.

Non-invasive markers of liver fibrosis are useful in excluding advanced fibrosis in heavy drinkers and those with the metabolic syndrome (obesity, type 2 diabetes mellitus, hyperlipidaemia, hypertension).[2]

Definitions

γ−Glutamyl transpeptidase (GGT)

An isolated raised serum GGT in the absence of a symptoms should be used to confirm that an elevated alkaline phosphatase (ALP) is of liver origin. An elevated GGT is not specific for alcohol misuse and also occurs in NAFLD. Non-invasive markers of liver fibrosis should be considered in individuals with metabolic risk factors for NAFLD and heavy drinkers.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

The upper limit of normal (ULN) for transaminases has been lowered over the last 5 years, and some groups consider 30 and 19 IU/litre to be the ULN for men and women, respectively. For the purpose of this article, the ULN is considered to be 40−45 IU/litre. Usually, results for either only ALT or AST are available, but having both can be helpful in both alcoholic liver disease (ALD) and cirrhosis, where the AST-to-ALT ratio is >1.0. ALT and AST also increase after muscle injury, which is usually recognized from an elevated serum creatine kinase concentration.

Alkaline phosphatase

Although there is some debate about the concentration of ALP requiring investigation, a threshold of 1.5 × ULN is usually used.

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Acute liver injury

Acute liver injury implies an abrupt injury occurring in a person with a previously healthy liver. If severe, it can present with jaundice, whereas ascites occurs only if there is acute hepatic vein obstruction (Budd–Chiari syndrome). Acute liver failure is a rare complication of acute injury, defined as coagulopathy and encephalopathy within 8 weeks of acute liver damage.

Chronic liver injury/cirrhosis

Chronic liver injury/cirrhosis can remain asymptomatic for years. It presents with ascites, variceal bleeding and hepatic encephalopathy. Jaundice in cirrhosis can be a reflection of gradual worsening of liver function associated with one of more of these complications. If associated with coagulopathy, it can be defined as chronic liver failure. Jaundice can also represent an acute deterioration in liver function in a cirrhotic patient; causes include sepsis, alcoholic hepatitis and reactivation of chronic hepatitis B infection. This syndrome often progresses rapidly to multiorgan failure and is known as acute-on-chronic liver failure.

Biliary injury

Biliary injury results from extrahepatic biliary disease caused, for example, by gallstones, or progressive intrahepatic biliary disease such as primary biliary cirrhosis (PBC). Both can present with jaundice.

Epidemiology

The most common causes of asymptomatic LFTs identified in general practice are NAFLD and ALD.[1] In contrast, the most common causes of jaundice presenting to both primary and secondary care are common bile duct stones and biliary malignancy, followed by a hepatocellular cause, most commonly alcoholic hepatitis.

History

Jaundice and itching

In jaundiced patients, dark urine and pale stools suggests large duct biliary obstruction, but these can also be present in severe hepatocyte injury such as acute viral hepatitis. Itching can occur with jaundice after large duct obstruction, intrahepatic biliary injury due to drugs, and occasionally severe hepatocellular injury resulting from acute hepatitis B infection. Itching preceding jaundice suggests intrahepatic biliary disease such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis.

Pain and weight loss

Severe abdominal pain does not occur in liver disease, although some patients complain of right upper quadrant discomfort. Episodes of right upper quadrant/epigastric pain in the presence of an elevated ALP suggest common bile duct stone(s), but ALT can also rise in this setting, as high as 1000 IU/litre in young patients with stones in a mildly dilated common bile duct. Pain is the key to the diagnosis. Weight loss classically occurs with malignancy but is also common in cirrhosis.

Other

Non-specific viral symptoms including myalgia and sore throat suggest an acute viral infection such as cytomegalovirus (CMV) or Epstein–Barr virus (EBV).

Drugs rarely cause chronic liver injury, but acute liver injury can occur from both prescribed and non-prescribed drugs (see Drug-induced liver injury, pages xx–xx of this issue).

A history of risk factors for chronic liver injury is important. Heavy alcohol intake and metabolic risk factors for NAFLD (hypertension, type 2 diabetes mellitus, hyperlipidaemia, increased body mass index (BMI)) can coexist and increase the risk of liver injury, as does coexistent chronic viral hepatitis and haemochromatosis.

It is important when taking a history to remember that elevated LFTs can reflect underlying systemic disease rather than primary liver disease. An elevated ALP is commonly seen in active rheumatoid arthritis and also in elderly individuals with right heart failure caused by hepatic congestion (Table 1). Elements of the history can help to indicate specific liver diseases (Table 2).

Examination

Hepatomegaly/splenomegaly

Clinical hepatomegaly is an indication for investigation however abnormal asymptomatic LFTs are. However, the absence of cutaneous stigmata of chronic liver disease does not exclude cirrhosis. In cirrhosis, the liver can be clinically small, normal size or enlarged. ALD often leads to a large liver, whereas in autoimmune liver disease the liver is often small. Splenomegaly suggests portal hypertension but may only be evident on ultrasound. Acute viral infections such as CMV and EBV can cause splenomegaly but are usually associated with systemic symptoms.

Ascites

Non-hepatic causes that justify exclusion include exudative malignant and pancreatic ascites (from pancreatic duct leak). Tuberculosis is another rare cause of an exudative ascites; ethnicity and travel history can help in diagnosis.

Cirrhosis and hepatic venous outflow obstruction cause a transudative ascites. The latter can be caused by right heart failure (elevated jugular venous pressure) or obstruction of the hepatic veins (sinusoidal outflow obstruction); it can be differentiated from cirrhosis by a high ascitic protein concentration. In acute hepatic vein obstruction (previously known as Budd–Chiari syndrome), there is a sudden onset of ascites and hepatomegaly with or without jaundice.

Systemic causes of abnormal LFTs

Elevated ALP	Polymyalgia rheumatica
	Hyper/hypothyroidism
	Active rheumatoid arthritis
	Systemic vasculitis
	Right heart failure
	Liver infiltration, caused by lymphoma, or sarcoid (granuloma)
Elevated ALT/AST	Coeliac disease
	Thyroid disease

Table 1

Hints from the history in investigating abnormal LFTs

History	Abnormal LFT	Possible diagnosis
Inflammatory bowel disease	ALP	PSC
Ethnicity/country of birth	ALT/AST	Hepatitis B/C
IVDU/unscreened blood transfusions	ALT/AST	Hepatitis C
Alcohol	ALT/mixed	Alcoholic disease
Metabolic syndrome (increased BMI ± diabetes/hypertension)[a]	ALT/AST	NAFLD
Recent new drugs	ALP or ALT	Drug-induced
Family history ± Knee or metacarpophalangeal joint pain		Haemochromatosis
± Emphysema		α_1-Antitrypsin
± Difficulty writing or concentrating		Wilson's disease

IVDU, intravenous drug use; PSC, primary sclerosing cholangitis.
[a] Around 30% of individuals with NAFLD have raised ALP concentrations.

Table 2

Initial investigations

The most common causes of asymptomatic elevated LFTs are ALD, NAFLD and drugs which including herbal remedies and over-the-counter medications.

Most hepatotoxic drug reactions occur within 1–2 months of starting a drug. There are some exceptions, such as tetracyclines given for acne, where reactions can occur up to 2 years later and can induce an autoimmune liver disease. Co-amoxiclav reactions often occur a few weeks after stopping the drug. In hepatitic drug reactions, LFTs usually return to normal over weeks, in contrast to cholestatic reactions where this can take months. It is important to ensure that LFTs return completely to normal after drug withdrawal, to exclude underlying coexistent chronic liver disease. Abnormal LFTs are common in patients taking statins but are usually caused by underlying NAFLD.

Further investigations

The pattern of LFTs dictates further investigations.

Synthetic liver function

Advanced liver disease is likely in the presence of a low platelet count or prolonged prothrombin time with or without a low serum albumin. These findings warrant investigation with an ultrasound scan and chronic liver disease screen even if ALP/ALT is normal or only slightly elevated.

Hepatitic liver function tests (Table 3)

Ultrasonography identifies abnormal liver texture and signs of portal hypertension such as splenomegaly. The presence of fat is common and does not always indicate liver injury. Persistently minor elevation in ALT (<100 IU/litre) is common in chronic hepatitis C and B, haemochromatosis and NAFLD.

Haemochromatosis should be excluded by measuring serum ferritin, which can be elevated as an acute-phase protein, and transferrin saturation, which is usually >55%. The diagnosis is confirmed by genetic testing for the *HFE* gene. Liver fibrosis assessment can be done non invasively i.e. with fibroscan with a liver biopsy reserved for those with intermediate scores and those with potential dual aetiologies. A serum ferritin is <1000 IU/ml is a negative predictor for liver fibrosis in the absence of other cofactors such as NAFLD and alcohol.

NAFLD is the most common cause of abnormal LFTs in the presence of a negative chronic liver disease screen and can progress to cirrhosis. NAFLD without liver fibrosis is more likely in the absence of diabetes mellitus, hypertension and elevated serum triglycerides (triacylglycerols); the use of non-invasive markers of liver fibrosis, which are a good negative predictor of liver fibrosis, means that a liver biopsy can be avoided.

In ALD, ALP and ALT are often elevated, but ALT is rarely >250 IU/litre; a higher concentration suggests coexistent liver injury such as inadvertent paracetamol toxicity. Although an AST-to-ALT ratio >1.0 is strongly suggestive of an alcoholic cause for the liver dysfunction, the ratio is also >1.0 in advanced liver fibrosis of any cause. ALT >1000 IU/litre suggests autoimmune liver disease,[3] acute viral hepatitis or drug injury. Hepatitis E is now recognized as a cause of endemic acute viral hepatitis. In autoimmune liver disease, serum immunoglobulin (Ig) G is often >30 g/litre and a liver biopsy is required to confirm the diagnosis. Very high ALT levels >10,000 are seen with ischaemic hepatitis and paracetamol liver injury.

The approach to the investigation of hepatitic LFTs in the presence of jaundice is similar, except that it is unusual for haemochromatosis or NAFLD to present with jaundice. Very high concentrations of ferritin are common in acute liver injury because of hepatocyte necrosis and inflammation, as occur in acute hepatitis A with jaundice. The most important differential diagnosis of jaundice with hepatitic LFTs is between acute viral hepatitis, drug-induced liver injury and autoimmune liver disease.

Cholestatic liver function tests

Whether or not the patient has jaundice, if ALP concentration is persistently ≥1.5 × ULN, an ultrasound scan of the liver should be performed to differentiate extrahepatic from intrahepatic biliary disease and to exclude hepatic infiltration resulting from liver metastases. Although bile duct stones are usually associated with pain, they can occur without symptoms, particularly if the duct is very dilated. If no cause for bile duct dilatation is identified by ultrasonography, magnetic resonance cholangiopancreatography (MRCP) should be performed. In the presence of jaundice, endoscopic retrograde cholangiopancreatography (ERCP) may be indicated as therapeutic intervention is likely to be needed.

In the absence of extrahepatic biliary obstruction, antimitochondrial antibodies (AMAs) should be checked to exclude PBC. These are positive in 90% of cases of PBC, patients usually being female. In AMA-negative individuals, MRCP should be carried out to exclude intrahepatic biliary disease such as primary sclerosing cholangitis (PSC); this should be followed by a liver biopsy if the diagnosis remains unclear. Other autoantibodies such as anti-glycoprotein-210 (anti-GP210) and anti-SP100 nuclear antigen (anti-SP100) can be positive in the 10% of patients with PBC who are AMA-negative.

Investigation of elevated ALT (hepatitic LFTs)

ALT <100 IU/litre
- Liver ultrasound
- Chronic liver disease screen
- Hepatitis B sAg
- Hepatitis C Ab or Ag
- Ferritin + transferrin saturation
- Liver autoantibodies (antinuclear factor, smooth muscle antibody)

Immunoglobulins
- α_1-Antitrypsin
- Endomysial antibody
- Copper/ceruloplasmin (if age <40 years)

ALT >100 IU/litre
- As above + consider a liver biopsy if diagnosis not clear

ALT >500 IU/litre
- Also consider acute viral hepatitis
- Hepatitis A immunoglobulin M (IgM)
- Monospot for Epstein–Barr virus infection
- Cytomegalovirus IgM
- Hepatitis E IgM

Ab, antibody; sAg, surface antigen.

Table 3

Systemic IgG4-related disease is a recently recognized, corticosteroid-responsive condition that can cause intrahepatic cholestasis (and mimic a hilar cholangiocarcinoma) or inflammation of the pancreas (autoimmune pancreatitis), leading to a distal bile duct stricture; its appearance on MRCP is similar to that of sclerosing cholangitis. The diagnosis is confirmed by the presence of IgG4 plasma cells on histology and/or an elevated serum IgG4.

Severe systemic sepsis can lead to intrahepatic cholestasis with jaundice and a high ALP concentration. This is commonly seen in intensive care settings and is a diagnosis of exclusion.

Jaundice

See Investigation of jaundice on pages 713–717 of this issue. A prolonged prothrombin time can reflect vitamin K malabsorption, which is common in biliary obstruction and occasionally seen in intrinsic liver disease. Therefore a repeat measurement after giving vitamin K can be helpful.

In prehepatic jaundice, ALT and ALP are normal and can be distinguished from cirrhosis with normal LFTs by the presence of a normal albumin, prothrombin time and platelet count. Once haemolysis has been excluded, Gilbert's syndrome is the likely explanation for hyperbilirubinaemia. Although serum bilirubin concentration rises with intercurrent illness or starvation in Gilbert's syndrome, it rarely exceeds 100 micromol/litre, in contrast to haemolysis.

Other blood tests

Plasma ammonia: this rises in hepatic encephalopathy but the concentration does not correspond to the degree of hepatic encephalopathy. In acute liver failure, it is helpful in assessing risk of cerebral oedema.

Tumour markers: an elevated serum CA125 concentration is common in cirrhosis and may not indicate that ascites is caused by gynaecological malignancy.

Serum α-fetoprotein (AFP) is elevated in 60% of patients with hepatocellular carcinoma but can be normal with small tumours. It can be useful in identifying hepatocellular carcinoma, which occurs in 1% of cirrhotic individuals per year. Hepatocellular carcinoma should be suspected in patients with previously undiagnosed cirrhosis who present with ascites or jaundice. AFP also rises in the presence of chronic hepatitis C infection. Very high concentrations are seen in acute liver injury, and AFP should be checked only in patients suspected of having cirrhosis or a liver mass.

Ascitic tap

A sample (10 ml) of ascitic fluid is crucial to confirm liver disease and exclude other causes (Table 4). It is always important to exclude infective ascites in cirrhosis by measuring the neutrophil count and placing ascitic fluid in blood culture bottles.

Liver biopsy

A liver biopsy is used to establish the cause of abnormal LFT and/or the degree of liver fibrosis.

Liver biopsy should be undertaken to exclude cirrhosis in patients with clinical hepatomegaly, thrombocytopenia, splenomegaly on ultrasound or stigmata of chronic liver disease, whatever the degree of elevation of LFTs. Identification of cirrhosis is important as it also leads to targeted screening for varices and hepatocellular carcinoma. Liver fibrosis is often patchy in biliary disease, and a liver biopsy is not indicated if there is a clear diagnosis.

Liver biopsy can usually be performed percutaneously, with a -morbidity of 0.4%. A transjugular liver biopsy is indicated in the presence of ascites, a platelet count $<80 \times 10^9$/litre and a prothrombin time prolonged by >4 seconds.

Non-invasive assessment of liver fibrosis[4]

The tests can be divided into blood tests that include biomarkers of liver fibrosis (e.g. FibroTest-ActiTest and the European Liver Fibrosis score) and non-serological tests, which include

Investigation of ascites

SAAG	<11.0 = exudate ≥11.0 = transudate
Protein	High in hepatic venous outflow obstruction despite SAAG ≥11.0 suggesting transudate
Neutrophil count	>250 cells/mm^3 in spontaneous bacterial peritonitis
Cytology	High yield in ovarian cancer
Amylase	Pancreatic duct leak in chronic pancreatitis of pancreatic injury
Triglyceride	Cloudy ascites can be chylous with elevated triglycerides rather than infective and can occur in cirrhosis

SAAG, Serum albumin–ascitic albumin gradient.

Table 4

Serological non-invasive markers of liver fibrosis

Test	Components of test
Fibrosis-4 (FIB-4) score	Age, AST, ALT, platelets
ELF	TIMP-1, PIIINP, hyaluronic acid
NAFLD fibrosis score	Age, BMI, AST, ALT, platelets, albumin, presence/absence of type 2 diabetes
FibroTest®	α2-Macroglobulin, haptaglobin, GGT, bilirubin, apolipoprotein A, gender, age

PIIINP, amino-terminal propeptide of type III collagen; TIMP1, tissue inhibitor of metalloproteinases 1.

Table 5

FibroScan®, magnetic resonance elastography or diffusion-weighted magnetic resonance imaging (MRI) (Table 5). FibroScan® delivers a pulse wave into the liver to quantify liver stiffness. Its advantage is that it is portable and can be used in clinic settings. Accurate readings are difficult to obtain in some individuals and with obesity, although different-sized probes have been developed in an attempt to deal with this. This problem can be overcome if MRI techniques are used instead, with the advantage that the whole liver can be visualized.

The current limitations of these tests is that they clearly differentiate only between mild fibrosis and cirrhosis. However, they are increasingly used in diagnostic algorithms to guide the need for liver biopsy to stage liver scarring[5] and treatment, for example for variceal screening in cirrhosis. All the tests have a very good negative predictive value for liver fibrosis, avoiding the need for liver biopsy in individuals unlikely to have advanced liver fibrosis, and where the cause of liver disease is known (e.g. chronic viral hepatitis).

The tests also have role in screening for advanced liver fibrosis in patients with risk factors for liver disease. This includes heavy drinkers of alcohol and patients with risk factors for NAFLD, for example individuals with type 2 diabetes who have fat on an ultrasound scan or elevated ALT levels with a negative chronic liver disease screen.

National Institute for Health and Care Excellence alcohol guidelines advocate that FibroScan® screening of women who drink >30 units/week and men who drink >50 units/week should be undertaken every 3–5 years irrespective of liver biochemistry. ◆

KEY REFERENCES

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 50-year-old man presented with a 4-week history of abdominal distention and weight loss. He drank 50 units beer/week. He was also taking metformin, atenolol and low-dose atorvastatin, which he had been on for 5 years. On clinical examination, he had a body mass index of 35 kg/m^2. The liver was enlarged 4 cm, and there was clinical ascites

Investigations

- Haemoglobin 10 g/litre (130–180)
- White cell count 8 × 10^9/litre (normal differential), (4.0–11.0)
- Platelets 130 × 10^9/litre (150–400)
- Bilirubin 22 micromol/litre (1–22)
- Alkaline phosphatase 135 U/litre (45–105)
- Alanine aminotransferase 100 U/litre (45–105)
- International normalized ratio 1.4 (<1.4)
- Albumin 28 g/litre (37–49)

What is the next most appropriate investigation?

A. Transient elastography (FibroScan®)
B. Aspartate aminotransferase concentration
C. Serum albumin–ascitic albumin gradient
D. Ascitic lactic dehydrogenase concentration
E. Percutaneous ultrasound-guided liver biopsy

Question 2

A 45-year-old woman presented with a 2-week history of feeling non-specifically unwell. She had been previously fit and had never had a blood transfusion, undergone surgery or used intravenous drugs. She was not taking any regular medication. Her sister had hypothyroidism. She was drinking one 750 ml bottle of gin every week. There were no abnormal findings on clinical examination.

Investigations

- Haemoglobin 13 g/litre (130–180)
- White cell count 8 × 109/litre (normal differential), (4.0–11.0)
- Platelets 400 × 109/litre (150–400)
- Ferritin 800 micrograms/litre (15–300)
- Transferrin saturation 20% (<25)
- Bilirubin 30 micromol/litre (1–22)
- Alkaline phosphatase 170 U/litre (45–105)
- Alanine aminotransferase 1860 U/litre (45–105)
- International normalized ratio 1.1 (<1.4)
- Albumin 40 g/litre (37–49)

What is the most likely diagnosis

A. Alcohol-related liver disease
B. Haemochromatosis
C. Cirrhosis caused by hepatitis B infection
D. Autoimmune liver disease
E. Wilsons disease

Question 3

A 56-year-old woman presented with a 2-month history of itching and fatigue. She was drinking 25 units of alcohol per week. Medication included simvastatin, which she had been taking for 2 years. On clinical examination, there were scratch marks. The body mass index was 24 kg/m^2, which was unchanged over 5 years. A community abdominal ultrasound scan was normal.

Investigations

- Haemoglobin 12 g/litre (130–180)
- White cell count 6 × 10^9/litre (normal differential), (4.0–11.0)
- Platelets 350 × 10^9/litre (150–400)
- Bilirubin 10 micromol/litre (1–22)
- Alkaline phosphatase 600 U/litre (45–105)
- Alanine aminotransferase 60 U/litre (45–105)
- γ-Glutamyl transferase 400 U/litre (4–35)
- International normalized ratio 1.0 (<1.4)
- Albumin 40 g/litre (37–49)

What is the next best test needed to make a diagnosis?

A. immunoglobulins
B. antimitochondrial antibody
C. Elastography
D. Fibrosis-4
E. Ferritin