Clinical and biochemical assessment of symptomatic and asymptomatic liver disease

Jane Collier

Abstract

Asymptomatic abnormal liver function tests (LFTs) are common, affecting 8% of the population. They are caused mainly 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 will help to exclude non-hepatic causes of abnormal LFTs as well as indicating a potential hepatic cause. Cirrhosis may present with ascites or jaundice, the latter being common in alcoholic liver disease as a result of added injury from alcoholic hepatitis. Investigations of 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 all 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 Western world as a cause of endemic acute hepatitis. Systemic IgG4 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; non-alcoholic fatty liver disease

What's new?

- Systemic immunoglobulin G4 disease/autoimmune pancreatitis should be considered in the differential diagnosis of cholestatic liver function tests
- Hepatitis E is endemic in the UK and is an important cause of acute viral hepatitis that mimics hepatitis A
- Acute liver failure is being seen increasingly due to reactivation of unrecognized chronic hepatitis B in patients treated with rituximab and other B-cell depleting therapies
- There is more widespread use/interest in the use of non-invasive markers of liver fibrosis for identifying patients with fatty liver disease and chronic viral hepatitis with a favourable prognosis
- The concept of acute-on-chronic liver failure is becoming more widely accepted

Frequency

Abnormal liver function tests (LFTs) are found in 8% of the general population.[1] LFT abnormalities in asymptomatic individuals may be transient; if repeated within 3 weeks, 30% of elevated alanine aminotransferase (ALT) concentrations and 17% of elevated serum alkaline phosphatase (ALP) concentrations will have returned to normal. It is impractical to investigate everyone with abnormal liver biochemistry and 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 will eventually present with symptoms that include jaundice, liver failure or complications of portal hypertension, such as ascites, variceal bleeding and hepatic encephalopathy.

Jane Collier *MD FRCP is a Consultant Hepatologist at John Radcliffe Hospital, Oxford, UK. Competing interests: none declared.*

Definitions

GGT (serum γ glutamyltranspeptidase)

An isolated raised GGT in the absence of a symptom does not require further investigation and should be used merely to confirm that an elevated ALP is of liver origin. An elevated GGT is not specific for alcohol misuse and also occurs in simple fatty liver disease (non-alcoholic fatty liver [NAFLD]).

ALT/AST (serum aspartate aminotransferase)

The upper limit of normal (ULN) for transaminases has been lowered over the last 5 years and some groups would consider 30 IU/L to be the ULN for men and 19 IU/L for women. For the purpose of this article the ULN is considered to be 40–45 IU/L. Usually only ALT or AST is available but having both can be helpful in both alcoholic liver disease and cirrhosis where the AST/ALT ratio is more than 1.0. Both ALT and AST also rise following muscle injury, which is usually recognized because of an elevated serum creatine kinase.

ALP

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

Acute liver injury

Acute liver injury implies an abrupt injury occurring in a person with a previously healthy liver. If severe, it may 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 may 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 may also represent an acute deterioration in liver function in a cirrhotic patient and

precipitants include sepsis, alcoholic hepatitis and reactivation of chronic hepatitis B infection; this syndrome often progresses rapidly to multi-organ failure and is now known as acute-on-chronic liver failure.[2,3]

Biliary injury

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

Epidemiology

The most common causes of asymptomatic LFTs identified in general practice are non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD).[4] 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.[5] NAFLD encompasses simple fat (NAFL) and fat with inflammation and fibrosis known as non-alcoholic steatohepatitis (NASH).

History

Jaundice and itching

In jaundiced patients, the presence of dark urine and pale stools suggests large duct biliary obstruction, but these features can also be present in severe hepatocyte injury such as acute viral hepatitis. Itching can occur with jaundice following large duct obstruction, intrahepatic biliary injury due to drugs, and occasionally severe hepatocellular injury due to acute hepatitis B infection. Itching preceding jaundice suggests intrahepatic biliary disease such as primary biliary cirrhosis 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 are suggestive of common bile duct stone(s), but it is worth remembering that ALT can also rise in this setting, as high as 1000 IU/L 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 are suggestive of acute viral infection such as cytomegalovirus (CMV) or Epstein–Barr virus (EBV) infections.

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 590–593 of this issue).

Although alcohol is the most common cause of chronic liver injury it is important to exclude other co-factors including NAFLD, chronic viral hepatitis and haemochromatosis.

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

Examination

Hepatomegaly/splenomegaly

Clinical hepatomegaly is an indication for investigation whatever the extent to which asymptomatic LFTs are abnormal. However, the absence of 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 be evident only on ultrasound. Acute viral infections such as CMV and EBV can cause splenomegaly but will usually be 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 in relation to which ethnicity and travel history may help in diagnosis.

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

Initial investigations

Repeat LFT

The most common causes of asymptomatic elevated LFTs are ALD, NAFLD and drugs. LFTs should be repeated 4–6 weeks after abstinence from alcohol, weight reduction if body mass index is elevated and cessation of any recently introduced drugs, 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, which can occur up to 2 years later and may

Systemic causes of abnormal LFTs

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

ALP, serum alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; LFTs, liver function tests.

Table 1