Case 14
A 64-year-old man with abnormal liver function tests

Mr Jack Reynolds is a 64-year-old man who has recently been discharged from hospital after treatment for pneumonia. The discharge letter requested follow-up of ‘abnormal liver function tests’ that were discovered during the inpatient admission. He has come to see you to have this looked into further.

What questions should you ask him?
Presenting complaint
You want to know whether the ‘abnormal liver function tests’ may have preceded or occurred during the admission to hospital. This may be related to sepsis, drugs or an underlying liver or biliary pathology.

Ask him questions about his admission to hospital. Specifically, what were his symptoms prior to admission, the duration and severity of illness, antibiotics given and new medications (especially hepatotoxic ones) started by his GP or in the hospital.

Accompanying symptoms
Ask him about symptoms that may give you a clue about possible aetiology:
• Has he experienced jaundice, abdominal pain, fever, pruritus or a change in urine and stool colour? A history of jaundice associated with the sudden onset of severe right upper quadrant pain and shaking chills suggests cholecodolithiasis and ascending cholangitis.
• Has he experienced jaundice before that resolved spontaneously? Consider Gilbert’s syndrome as a cause of hyperbilirubinaemia in the context of a concurrent illness.
• Does he have arthralgia, myalgia or a rash? A history of arthralgia and myalgia predating jaundice suggests viral or drug-related hepatitis.
• Has he lost his appetite and experienced weight loss? Malignancy must be considered, either as a primary or secondary involvement.
• Is there evidence of abdominal swelling of ascites or fluid retention? Does he get breathless on exertion or lying flat? This may occur in decompensated cirrhosis or congestive heart failure (transudate) or be in keeping with malignancy, or infective or inflammatory conditions (exudates).

Medical history
• Does he have a previous history of gallstone disease, liver disease or cardiac failure?
• Does he have a history of malignancy?

Medications
Has he been exposed to any chemicals, prescribed medication or over-the-counter medication that may be temporally related to the onset of liver function abnormalities? In addition, herbal preparations and illicit drug use must be considered.

Common causes of abnormal liver function tests (LFTs) include non-steroidal anti-inflammatory drugs, paracetamol, antibiotics, statins, antiepileptic drugs and antituberculous drugs. In particular consider antibiotics in this man with recent pneumonia.

Social history
• Risk factors for hepatitis B and C. Has he ever had a blood transfusion (when and where), a tattoo, used intravenous drugs or had high-risk sexual activity?
• Risk factors for hepatitis A. Has he travelled to, or lived abroad in, an area with endemic hepatitis?
• Risk factors for hepatotoxins. Has he had occupational exposure? Has he been exposed to contaminated foods?
• Alcohol-related liver disease. What is his alcohol consumption on a weekly basis? Is the alcohol history reliable?

**Family history**
• Is there a family history of jaundice or liver disease?

**Previous medical records**
• What is the duration and pattern of liver function abnormalities?
• Has his liver function been investigated before in the past and if so, what tests have been done?

He explains that he was in hospital for just 5 days requiring intravenous antibiotics to treat his pneumonia and was put on oral tablets thereafter. He has been out of hospital for 2 weeks and feels much better with a residual cough only. He cannot remember the name of the antibiotics but has a discharge letter with him. The letter tells you he was taking co-amoxiclav and clarithromycin for a total of 7 days, and used ibuprofen and paracetamol regularly for pleuritic pain.

He has a past history of type 2 diabetes, hypertension and hypothyroidism. He takes metformin, bendroflumethiazide and levothyroxine. He takes no over-the-counter medications or herbal treatments. He is a non-smoker and drinks a ‘moderate’ amount of alcohol, five bottles of beer a night. He has recently travelled to South India with his wife, staying in Kerala for a 2-week vacation. He has never had any known contact with hepatitis or been exposed to parenteral transfusions, drugs or tattoos. There is no family history of liver disease. His mother had thyroid disease and diabetes.

His liver function was checked over a year ago at his previous GP practice and he was not told of any abnormality in his liver tests then.

**What do you look for on examination?**

**General examination**
• Are there any stigmata of chronic liver disease?
• Are there signs suggestive of malignancy?
• Are there signs of longstanding disease, such as proximal muscle wasting?

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**Box 14.1 Stigmata of chronic liver disease**
• Spider naevi, located above the nipple line (see Plate 14.1)
• Palmar erythema
• Digital clubbing
• Dupuytren’s contractures
• Icteric sclera and skin
• Parotid gland enlargement
• Gynaecomastia
• Loss of axillary hair
• Caput medusae
• Abdominal ascites (portal hypertension)
• Splenomegaly (portal hypertension)
• Testicular atrophy

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**Box 14.2 Signs suggestive of malignancy**
• Weight loss (loose skin folds or clothes)
• Craggy lymphadenopathy
• Virchow’s node (left supraclavicular node) or periumbilical nodule suggestive of abdominal malignancy

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**Cardiac and respiratory examination**
• Jugular venous pulse: is there jugular venous distension? This is a sign of right-sided heart failure, suggesting hepatic congestion.
• Pleural effusion (unilateral or bilateral): bilateral pleural effusions support cardiac failure. A right pleural effusion, in the absence of clinically apparent ascites, may be seen in advanced liver cirrhosis, malignancy or represent a para-pneumonic effusion.

**Abdominal examination**
• Feel for the size of the spleen (a palpable spleen is enlarged).
• Percuss for ascites. Is there a fluid wave or shifting dullness? Ascites in the presence of jaundice
suggestions either cirrhosis or malignancy with peritoneal spread.

- Abdominal mass or tenderness. Severe right upper quadrant tenderness with respiratory arrest on inspiration (Murphy’s sign) suggests cholecystitis or, occasionally, ascending cholangitis. A gallbladder or mass may be palpable.

On general examination he is overweight (BMI 29) with no stigmata of chronic liver disease. He has tanned skin but no scleral jaundice. On auscultation of his chest there are some inspiratory coarse crepitations at the right base with no clinical signs of effusion. Abdominal examination confirms a large distended abdomen which is soft and non-tender, with no palpable organomegaly or ascites.

What is your differential diagnosis based on the information so far?

- Drug-induced (antibiotics, non-steroidal drugs, paracetamol) liver disease. The temporal relationship between medication and hepatotoxicity can be difficult to define but gradually resolves with removal of the offending agent.
- Sepsis-related pneumonia. Tests should normalise once the infection has resolved.
- Hepatic steatosis or steatohepatitis, based on co morbidities, BMI and physical examination.
- Alcohol-related liver disease. He consumes over 35 units/week of alcohol, which can lead to progressive liver damage.
- Haemochromatosis; He has bronzed skin (perhaps related to iron overload or his recent holiday in India).
- Viral hepatitis, based on his travel history.
- Autoimmune liver disease, based on his history of other autoimmune conditions such as diabetes and thyroid disease and family history (although very rare in men).

How do you investigate this man further?

Liver chemistry (colloquially known as liver function tests or LFTs)

What was the initial abnormality in liver function and is it persistent? The liver chemistry should be repeated to determine a pattern.

The most commonly tested aspects of liver chemistry are:

- Enzyme tests:
  - Transaminases: serum aminotransferases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)).
  - Bile duct-expressed enzymes: alkaline phosphatase (ALP) and $\gamma$-glutamyl transferase ($\gamma$-GT).
  - Serum bilirubin, which measures the liver’s ability to detoxify metabolites and transport organic anions into bile.
  - Serum albumin, which is a test of hepatic synthetic function.

Additional critical information on hepatic function is obtained from the prothrombin time (PT), which depends on the synthesis of clotting factors in the liver, and is prolonged in liver disease, and in cases of vitamin K deficiency, which can be a consequence of biliary obstruction and consequent malabsorption of fat and fat-soluble vitamins.

Diseases causing hepatocellular injury typically cause a disproportionate elevation in serum ALT and AST compared with the ALP and $\gamma$-GT. An example is hepatitis.

Diseases causing biliary damage or cholestasis typically cause a disproportionate elevation in serum ALP and $\gamma$-GT compared with the AST and ALT. These patterns often overlap.

The serum bilirubin can be elevated in both hepatocellular and cholestatic conditions and therefore is not necessarily helpful in differentiating between the two.

The serum albumin and PT are useful to assess liver function. Low albumin suggests a chronic process such as cirrhosis or cancer. Normal albumin suggests a more acute process such as viral hepatitis or choledocholithiasis. Elevated PT indicates either vitamin K deficiency due to malabsorption or significant hepatocellular dysfunction. The failure of the PT to correct with parenteral administration of vitamin K indicates severe hepatocellular injury.

KEY POINT

- A complete history supported by an examination to look for signs of liver disease is the best method of determining the cause of abnormal liver function tests. The pattern of liver abnormalities and their fluctuation over time is important.

On general examination he is overweight (BMI 29) with no stigmata of chronic liver disease. He has tanned skin but no scleral jaundice. On auscultation of his chest there are some inspiratory coarse crepitations at the right base with no clinical signs of effusion. Abdominal examination confirms a large distended abdomen which is soft and non-tender, with no palpable organomegaly or ascites.
Individual patients can have baseline fluctuation in aminotransferases. Chronic (more than 6 months) persistent ALT elevations require further investigation.

How do you investigate an abnormal ALT?

Risk factors

Medications

The relationship between drug ingestion and toxicity is not always clear; patients may take multiple medications making the offending agent difficult to recognise, have concomitant diseases (such as alcoholism) that produce similar clinical/laboratory abnormalities, and may have a delay in the onset of hepatotoxicity. Features suggesting drug toxicity include lack of illness prior to ingesting the drug, clinical illness or biochemical abnormalities developing after beginning the drug, and improvement after the drug is withdrawn. The abnormalities will generally recur upon reintroduction of the offending substance, but re-challenge is generally not advised.

Alcohol abuse

The diagnosis of alcohol abuse can be difficult because many patients conceal this information. Several short questionnaires are of assistance (such as the CAGE questionnaire). Patterns of abnormalities supportive of alcohol abuse include an AST to ALT ratio of 2:1 or greater, and a two-fold elevation of the \( \gamma \)-GT in patients with an AST to ALT ratio greater than 2:1. It is unusual for the ALT to be greater than five-fold elevated. The ALT may even be normal in patients with severe alcoholic liver disease.

Hepatic causes of elevated ALT/AST

Viral hepatitis

This includes hepatitis A, B, C and E and cytomegalovirus (CMV) or Epstein–Barr virus (EBV) hepatitis.

- **Hepatitis B.** The risk is increased in patients with a history of parenteral exposure and travel to or residence in areas of high disease prevalence, such as South-East Asia, China and sub-Saharan Africa. Initial testing for patients suspected of having chronic hepatitis B is hepatitis B surface antigen (HBsAg), surface antibody (HBsAb) and core antibody (HBeAb).

Patients who are HBsAg and HBeAb positive are chronically infected. Additional testing in this group includes hepatitis B ‘e’ antigen (HBeAg) and ‘e’ antibody (HBeAb) and a hepatitis B virus (HBV) DNA. The presence of a positive HBV DNA in the presence or absence
of HBeAg indicates viral replication. A positive HBV DNA and a negative HBeAg indicates a pre-core mutant. Both of these situations warrant further evaluation with a liver biopsy and possible treatment.

A positive HBsAg and a negative HBsAb and HBeAg suggests that the patient is a carrier of hepatitis B in a non-replicative state. The presence of a carrier state does not explain elevated aminotransferases and another cause needs to be found. A positive HBsAb and HBeAb suggests immunity to hepatitis B and another cause of aminotransferase elevation should be sought.

- **Hepatitis C**. The risk is increased in individuals with a history of parenteral exposure (blood transfusion, intravenous drug use, occupational), cocaine use, tattoos, body piercing and high risk sexual behaviour. The initial test for hepatitis C is the hepatitis C antibody (HCV Ab).

A positive HCV Ab in a patient with risk factors for the infection is sufficient to make the diagnosis, and a quantitative hepatitis C virus (HCV) RNA, HCV genotype and liver biopsy should be done to assess the patient’s need and suitability for treatment. A positive HCV Ab in a low risk patient should be verified with either a HCV recombinant immunoblast assay (RIBA) test or a qualitative polymerase chain reaction (PCR) test. A negative HCV Ab in a patient with risk factors for hepatitis C should be verified with a qualitative PCR test.

**Hereditary haemochromatosis (HHC)**

Screening is by serum iron and total iron-binding capacity (TIBC), allowing the calculation of the transferrin saturation (serum iron/TIBC). An iron saturation of greater than 45% warrants serum ferritin evaluation. Ferritin is an acute phase reactant and therefore is less specific than the iron saturation. A serum ferritin concentration of >400 ng/mL in men and >300 ng/mL in women further supports the diagnosis of HHC.

Genetic testing (HFE genotype) has not replaced liver biopsy in the diagnosis of HHC. C282Y/C282Y and C282Y/H63D are responsible for 95% of genetic haemochromatosis. Not every patient who is homozygous for the HFE mutation has iron overload and not every patient with HHC has the identified HFE mutation. Thus, the biopsy may still be required to identify iron overload in some patients and is critical to determine the amount of fibrosis.

A liver biopsy should be performed if screening tests suggest iron overload to quantify hepatic iron and to assess the severity of liver injury. A hepatic iron index greater than 1.9 is consistent with homozygous HHC. Liver biopsy is not necessary for patients aged less than 40 years with genotypically defined haemochromatosis (C282Y homozygous) with normal liver function tests.

Patients with HHC and cirrhosis continue to have a high risk of developing hepatocellular carcinoma (HCC) even with depletion of body iron stores. These patients need to be identified and screened with AFP measurements and ultrasound evaluation for liver lesions as appropriate (usually 6 monthly if there is cirrhosis).
Non-alcoholic steatohepatitis
NASH is more common in women and is associated with obesity and type 2 diabetes mellitus. The ratio of AST to ALT is usually less than one. The presence of fatty infiltration of the liver can be seen radiologically by ultrasound, CT imaging or MRI. However, radiological imaging cannot identify inflammation.

The differentiation between steatosis and NASH requires a liver biopsy (Fig. 14.1). This should be done in the presence of the following features: peripheral stigmata of chronic liver disease, splenomegaly, cytopenia, abnormal iron studies, diabetes and/or significant obesity in an individual over the age of 45 years. There is no effective medical therapy for NASH.

Autoimmune hepatitis (AIH)
This is found predominantly in young to middle-aged women. The diagnosis is based upon the presence of elevated serum aminotransferases, the absence of other causes of chronic hepatitis and features (serological and pathological) suggestive of AIH. A useful screening test is the serum protein electrophoresis (over 80% of patients with AIH will have hypergammaglobulinaemia). Additional tests include antinuclear antibodies (ANAs), anti-smooth muscle antibodies (anti-SMAs) and liver-kidney microsomal antibodies (LKMAs).

Elevated γ-globulins and high titre of autoantibodies should prompt a liver biopsy to confirm the diagnosis of AIH. If the biopsy is consistent with chronic active hepatitis, patients should receive a trial of corticosteroids.

Wilson’s disease
This is a genetic disorder of biliary copper excretion (Table 14.1), and may cause elevated aminotransferases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Homozygote frequency</th>
<th>Gene frequency</th>
<th>Heterozygote frequency</th>
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<tr>
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<tr>
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<tr>
<td>Wilson’s disease</td>
<td>1:30000</td>
<td>1:170</td>
<td>1:85</td>
</tr>
</tbody>
</table>

Table 14.1 Prevalence of inherited liver diseases. (From Leggett et al., 1990.)
in asymptomatic patients. Patients usually present between the ages of 5 and 25 years, but case reports document patients from 3 to 80 years old.

The initial screening test is serum ceruloplasmin (reduced in approximately 85%). Patients should be examined by an ophthalmologist for Kayser–Fleischer rings. If the ceruloplasmin is normal and Kayser–Fleischer rings are absent, a 24 h urine collection for quantitative copper excretion can be done; a value of greater than 100 µg/day is suggestive of the diagnosis.

The diagnosis is usually confirmed by a liver biopsy for quantitative copper. Patients with Wilson’s disease have liver copper levels of greater than 250 µg/g of dry weight.

**Alpha-1 antitrypsin deficiency**

In adults, α₁-antitrypsin deficiency should be suspected in patients who have a history of emphysema either at a young age or out of proportion to their smoking history. Decreased levels of α₁-antitrypsin can be detected either by direct measurement of serum concentrations or by the absence of the α₁ peak on serum protein electrophoresis.

**Non-hepatic causes of elevated ALT/AST**

**Muscle disorders**

Serum AST and ALT may both be elevated with muscle injury. Their ratio depends upon when they are assessed relative to the muscle injury. Consider subclinical inborn errors of muscle metabolism, polymyositis, seizures and heavy exercise such as long distance running. Determine the serum levels of creatinine kinase, lactate dehydrogenase (LDH) and aldolase (elevated at least to the same degree).

**Thyroid disorders**

Thyroid disorders can produce an elevated ALT/AST, although the mechanism is unclear. A TSH is a reasonable screening test for hypothyroidism while a full set of thyroid function tests should be checked if hyperthyroidism is suspected.

**Coeliac disease**

Elevated serum aminotransferases can occur in patients with undiagnosed coeliac disease. Liver tests return to normal when the patient is compliant with a gluten-free diet. Coeliac disease can be tested for by antibody screening (EMA, IgA antibody) and, definitively, by distal duodenal biopsies.

**Adrenal insufficiency**

Elevated ALT/AST levels (1.5–3 times the upper limits of normal) have been described in patients with adrenal insufficiency due to Addison’s disease or secondary causes. Liver tests normalise with appropriate treatment.

**Anorexia nervosa**

This has been associated with aminotransferase elevation by mechanisms that are not well understood.

Mr Reynolds went on to have a full liver screen and abdominal ultrasound. The liver screen was negative for hepatitis and autoimmune disease. His immunoglobulins, ferritin and AFP were normal. An abdominal ultrasound showed evidence of fatty infiltration of the liver with a normal spleen and no free fluid.

Additional tests revealed a normal TSH, EMA and creatinine kinase level. He had an appropriate cortisol response to a synacthen test.

**What is the most likely diagnosis and how would you manage this?**

The most likely diagnosis is hepatic steatosis or NASH, based on the isolated abnormal ALT, normal liver screen, fatty liver on ultrasound and his co-morbidities.

He should be advised to reduce weight by reducing the consumption of fatty foods and overall calorie intake (this may be guided by a dietician) and increase his daily exercise (Fig. 14.2). He should reduce his alcohol consumption to within the recommended limits, and ideally

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**Define risk factors:**

- Evaluate BMI
- Fasting glucose
- Fasting lipid profile
- Medications

**Goals:**

- Controlled weight loss
- Treat diabetes
- Treat hyperlipidaemia
- Stop toxic meds and alcohol

**Re-evaluate:**

- Repeat liver tests
- Monitor weight and lipids
- US liver
- Consider liver biopsy

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**Fig. 14.2** The management of NAFLD.
stop drinking all together given the contribution of alcohol to his liver disease.

He needs better control of his diabetes; consider gliclazide or a thiglizsome. He should control his blood pressure, with the addition of antihypertensive medication such as an angiotensin-converting enzyme (ACE) inhibitor. This medication is particularly important in the context of his diabetes, as an ACE inhibitor may help to control progression of disease and preserve his renal function. He should have a lipid profile taken, be given dietary advice for cholesterol reduction and may ultimately need a statin to lower the ALT level.

Patients who are at risk of progression to cirrhosis should be considered for biopsy.

Independent risk factors for fibrosis and/or cirrhosis (Day, 2002)

- Age >45 years.
- ALT more than two times normal.
- AST:ALT ratio >1.
- Obesity, particularly truncal.
- Type 2 diabetes or impaired glucose intolerance.
- Insulin resistance.
- Hyperlipidaemia (triglycerides >1.7).
- Hypertension.
- Iron overload.
- Hypertriglyceridaemia.

What next? Do you continue to observe or proceed to liver biopsy?

When should you watch and wait?

Observation is probably appropriate in those in whom the ALT and AST are less than two-fold elevated and no chronic liver condition has been identified by non-invasive testing.

When should you consider liver biopsy?

A liver biopsy should be considered in those in whom the ALT and AST are persistently greater than two-fold elevated and the cause remains undefined. Although it is unlikely that the biopsy will provide a diagnosis or lead to changes in management, it reassures the patient and physician to know that there is no serious underlying disorder. At biopsy, the most frequent finding is non-alcoholic steatohepatitis or fatty liver (in two-thirds of cases). A biopsy should not be undertaken without due consideration of the risk:benefit ratio. The risk of significant bleeding, morbidity and mortality from percutaneous liver biopsy is 1:1000.

He stopped drinking alcohol, reduced the fat in his diet and started to walk every morning to collect the newspaper (15 min per day). He lost 4.5 kg over 3 months. His ALT fluctuated, but remained elevated between 80 and 110 IU/L over the next 6 months.

He was referred for an ultrasound guided liver biopsy. There were no complications. He returned to clinic 2 weeks later. The liver biopsy confirmed fatty liver with no evidence of fibrosis or cirrhosis. Diet and exercise were reinforced. He was discharged back to your care.
CASE REVIEW

Abnormal liver function tests are may be identified incidentally on blood testing for other reasons. There are many liver-related and unrelated causes. The key is in the history to identify predisposing factors, and examination to support this.

Causes of abnormal liver function include medications, liver disease, cardiac failure, alcohol consumption, infection, malabsorption and many others. Investigations should be done to find the cause using the least invasive tests possible.

Non-alcoholic fatty liver disease is becoming increasingly prevalent in the Western world. Risk factors should be identified and treated. Goals include controlled weight loss, control of diabetes and hyperlipidaemia, and stopping alcohol and toxic medications. Liver biopsy may be needed in some patients to identify a progression to steatohepatitis, fibrosis and cirrhosis.

KEY POINTS

- Liver tests include enzyme tests (ALT, AST, ALP, γ-GT), serum bilirubin and measures of synthetic function (albumin and PT).
- A complete medical history is the most important part of the evaluation.
- The physical examination should focus upon findings suggesting the presence of liver disease.
- It is essential to determine the overall pattern of abnormal LFTs, which can be broadly divided into two categories: (1) patterns predominantly reflecting hepatocellular injury, and (2) patterns predominantly reflecting cholestasis.
- Many abnormal liver tests will return to normal spontaneously.
- Specific tests should be guided by the pre-test probability of the underlying liver disease, the pattern of abnormalities, and suggestive features obtained from the history and physical examination.
- The majority of patients in whom the diagnosis remains unclear after obtaining a history and laboratory testing will usually have alcoholic liver disease, steatosis or steatohepatitis.