Evaluating patients who have abnormal liver tests

Each month we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Liver tests are commonly performed as part of routine screening investigations. Estimations of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) are traditionally referred to as 'liver function tests'. This term is a misnomer because serum enzyme levels do not reflect liver function. More accurately, these tests should be termed 'liver tests'. Biochemical indices of liver 'function' include the serum bilirubin (reflecting hepatic excretory function) and estimations of serum albumin and prothrombin time (indicative of hepatic synthetic function). In the context of liver disease, a low platelet count suggests impaired liver function with concomitant portal hypertension.

History and examination

The initial step in evaluating a patient with raised liver enzymes is to undertake a thorough history and physical examination (Table 1), with particular emphasis on risk factors for liver disease. This includes a detailed history of alcohol intake, recreational drug use and ingestion of allopathic and traditional medications, including vitamins and herbal preparations. A family history of liver disease and personal history of intercurrent illnesses, in particular diabetes mellitus, should also be sought. The ingestion of drugs, particularly antibiotics, during the preceding three months needs to be elicited because liver injury may manifest several weeks after drug cessation. Risk factors for viral hepatitis must be elicited, such as intravenous drug use and, in migrants, country of origin.

The presence of any persistent abnormality of liver tests warrants further assessment. The degree and pattern of elevation will provide clues to the cause and may dictate the urgency of further investigations (see the flowchart on page 60). Marked elevations of ALT and AST demand urgent attention.

Interpreting patterns of liver test abnormalities

Any elevation in aminotransferase levels may signify liver injury. Liver test abnormalities are:

- 'hepatocellular' when the serum ALT is more than twice the upper limit of normal or R ≥5, where R is (number of times serum ALT is raised above the upper limit of its normal) divided by (number of times serum ALP is raised above the upper limit of its normal)

IN SUMMARY

- **Liver enzyme abnormalities may be physiological or pathological.**
- **Any persistent elevation of liver test results must be investigated.**
- **The cause of liver test abnormalities in the majority of cases can be determined by eliciting a detailed history and performing a thorough physical examination.**
- **Assess the degree as well as the pattern of elevation of liver tests.**
- **Serological testing for common causes of liver dysfunction should be undertaken.**
- **Upper abdominal ultrasonography is a useful noninvasive imaging procedure.**
- **Liver biopsy should be considered in consultation with a gastroenterologist.**

- 'cholestatic' if the serum ALP is more than twice the upper limit of normal or R ≤2
- 'mixed' in pattern when both ALT and ALP are raised, and R is between 2 and 5.

The ratio R may vary during the course of liver injury.

Causes of hepatocellular and cholestatic liver enzyme abnormalities are listed in Table 2.

In the vast majority of patients with liver disease, the serum ALT exceeds that of the AST. Notable exceptions include patients with alcoholic liver disease and those with cirrhosis.

Liver test abnormalities in association with a low serum albumin or prolonged prothrombin time signal significantly impaired hepatic synthetic function, while an elevated bilirubin reflects hepatic excretory dysfunction.

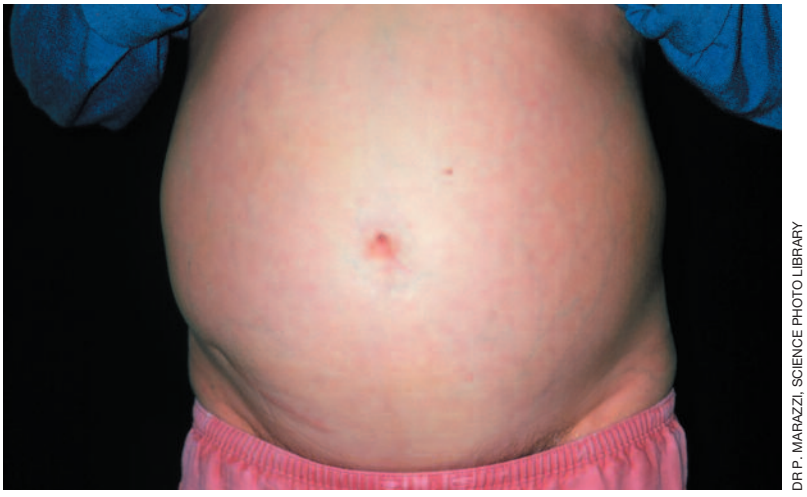

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Figure 1. Ascites in a 55-year-old woman who has alcohol-related liver damage.

Elevated aminotransferase levels

Aminotransferase levels are sensitive indicators of hepatic injury. Both ALT and AST are present normally in serum at low levels, usually less than 30 to 40 U/L. The normal range varies widely between laboratories. AST is found in liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leucocytes and erythrocytes. In muscle injury, the serum creatine kinase (CK) level is raised in parallel with AST. The highest levels of ALT reside in the liver. Thus, an elevation of this enzyme is a more specific indicator of liver injury than that of AST. However, both AST and ALT are released into the circulation in increasing amounts when liver cells are damaged.

Careful history taking is crucial in identifying the common causes of a predominantly hepatocellular pattern of liver enzyme abnormalities. They

Table 1. Physical signs of chronic liver disease

Jaundice
Foetor hepaticus
Finger clubbing
Palmar erythema
Flapping tremor
Spider naevi
Bruising
Scratch marks (a response to itchy skin)
Purpura
Muscle wasting
Ankle oedema
Feminisation (e.g. loss of body hair) in men
Enlarged or reduced liver
Enlarged spleen
Ascites (Figure 1)
Prominent veins in abdominal wall

Table 2. Causes of raised liver enzyme levels

Hepatocellular pattern
Alcohol abuse
Drug induced liver injury
Chronic hepatitis B and C
Nonalcoholic fatty liver disease
Haemochromatosis
Autoimmune hepatitis
Wilson's disease
Alpha-1-antitrypsin deficiency
Cholestatic pattern
Choledocholithiasis
Drug induced liver injury
Primary biliary cirrhosis
Primary sclerosing cholangitis
Neoplastic infiltration of the liver
Pancreatic cancer
Sarcoidosis

include alcohol-related liver disease, hepatitis B and C, nonalcoholic fatty liver disease, drugs and haemochromatosis (Table 2). Additional blood tests that are useful in identifying these disorders are listed in Table 3. Although a variety of liver diseases may cause sudden marked elevations in aminotransferase levels, viral, drug-induced and ischaemic hepatitis need to be excluded.

The causes of elevated aminotransferase levels are discussed in the following sections.

Alcohol-related liver disease

The diagnosis of alcohol abuse may be difficult because many patients conceal their true alcohol intake. The diagnosis of alcohol-related liver disease is supported by a ratio of AST to ALT of at least 2. The increased ratio reflects the low serum activity of ALT in patients with alcoholic liver disease due to a deficiency of pyridoxal-5-phosphate.

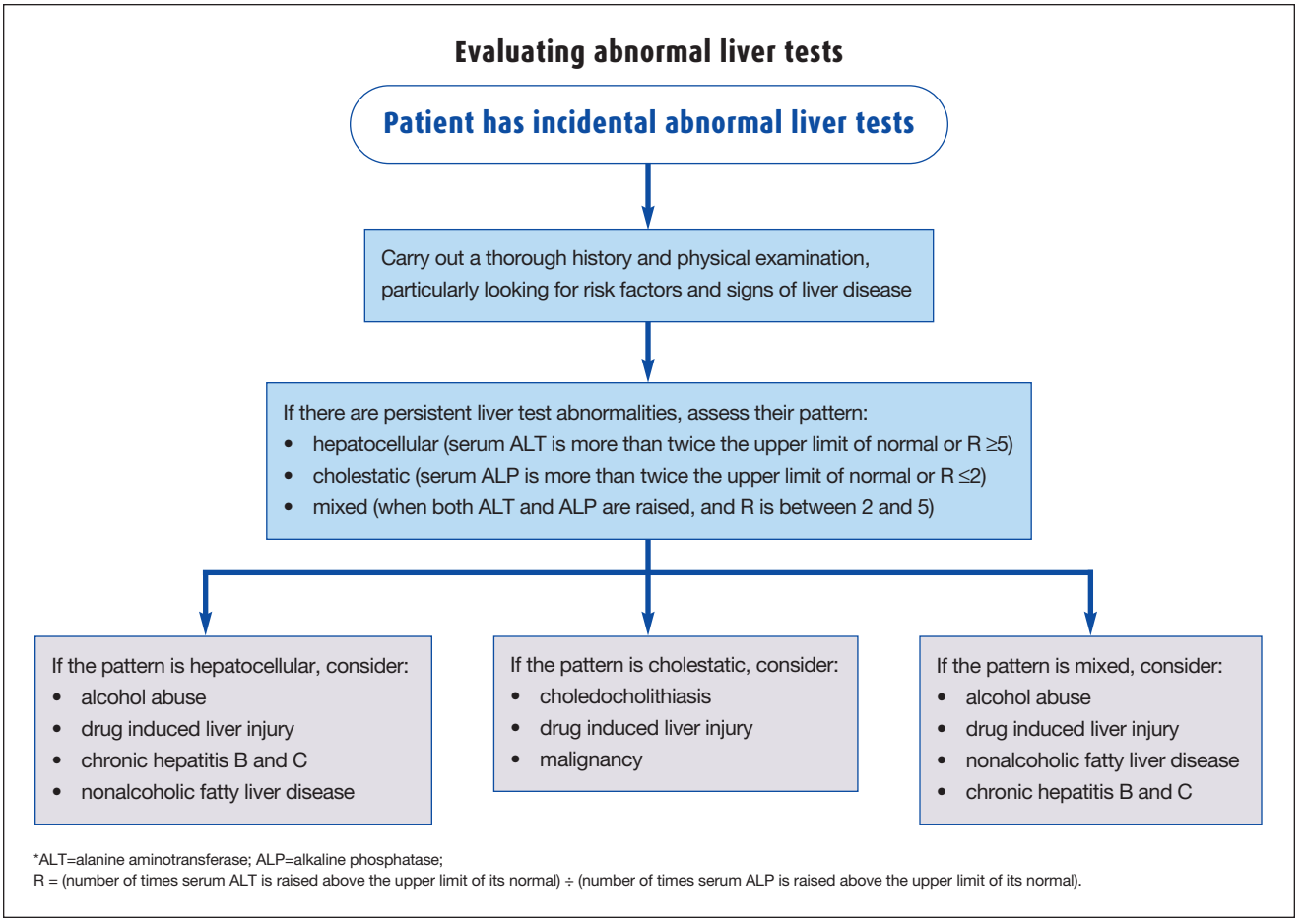
The degree of elevation of aminotransferase levels may provide further evidence for or against a diagnosis of alcohol-related liver disease. It is rare in patients with alcohol abuse for AST levels to be greater than eight times the normal value, and even less common for ALT levels to exceed five times the normal value. In fact, ALT levels may be normal in patients with severe alcohol-related liver disease. ALT levels greater than 300 U/L in patients with significant alcohol intake usually indicate the presence of another cause for the liver enzyme elevation, such as coincident paracetamol toxicity or viral liver disease.

The measurement of GGT provides useful corroborative evidence of alcohol abuse. A GGT level that is twice normal in patients with an AST:ALT ratio of at least 2 strongly implicates alcohol as the likely cause of liver enzyme abnormalities. However, the lack of specificity of GGT precludes its use as a single test to diagnose alcohol abuse.

Hence, laboratory features suggestive of alcohol abuse are an AST:ALT >2, ALT <300 U/L and an elevated GGT. Additional indicators of excessive alcohol consumption are a raised mean corpuscular volume and thrombocytopenia that corrects itself following alcohol abstinence.

Drug induced liver disease

Meticulous history taking and review of laboratory data are critical in diagnosing drug induced liver disease. Almost any



*ALT=alanine aminotransferase; ALP=alkaline phosphatase;
R = (number of times serum ALT is raised above the upper limit of its normal) ÷ (number of times serum ALP is raised above the upper limit of its normal).

medication can cause abnormal liver tests. Drug induced liver disease may mimic any type of liver disease histologically. A drug effect is possible if the rise in liver enzyme levels is associated with the commencement of a medication. It is important to note that changes in liver tests may persist long after cessation of the offending agent.

Commonly implicated drugs are listed in Table 4. The use of herbal preparations and illicit substances may also cause elevations in liver tests (details of which are fully discussed in a review by Chitturi and Farrell[1]).

The simplest way to determine whether a drug is responsible for the liver enzyme abnormality is to cease the suspected agent and follow liver tests serially, looking for a return to normal levels.

Chronic viral hepatitis

Chronic hepatitis C afflicts 0.5 to 1% of Australians; 85% of incident cases are related to previous intravenous drug abuse.

Since the introduction of second-generation enzyme immunoassays for hepatitis C virus antibody in blood products, new cases of transfusion-acquired hepatitis C are now rare. However, patients who received blood transfusions prior to February 1990 are at risk of hepatitis C virus infection.

People who are born in countries where there is a high prevalence of hepatitis C (such as South East Asia, the Mediterranean region, the Middle East, Africa and South America) are at high risk of acquiring hepatitis C. Other risk factors for hepatitis C are: being tattooed or body pierced, snorting cocaine, exposure to nonsterile instruments including acupuncture needles, needle stick injury and being born to hepatitis C virus infected mothers.

With the advent of more effective antiviral therapies (sustained response rates approach 50%), it is important to make the diagnosis of chronic hepatitis C infection and to consider referring this group of patients for specific therapy.

A hepatitis C antibody test is the initial diagnostic investigation in suspected cases. Tests in current use have a sensitivity of 92 to 97% in at risk populations. In a patient with risk factors, a diagnosis of chronic hepatitis C infection is suggested by a repeatedly positive hepatitis C antibody test and a raised ALT. However, up to 30% of patients with a positive antibody result have no ongoing viraemia, particularly if the ALT is persistently normal. The positive antibody result in this instance merely reflects previous exposure to the virus.

Confirmation of chronic hepatitis C infection can be obtained by the detection of hepatitis C virus RNA in serum. A liver biopsy (Figure 2) should be considered to assess the severity of liver damage in any hepatitis C viraemic patient with an elevated ALT. These individuals should be considered for antiviral therapy. Patients who are viraemic with persistently normal ALTs are currently not eligible for treatment, but they should be monitored.

Chronic hepatitis B results when immune elimination does not occur after acute infection and the hepatitis B virus continues to replicate. At risk populations include those from countries with high hepatitis B endemicity (e.g. South East Asia), indigenous Australians and individuals with a history of intravenous drug use. Hepatitis B serological tests include hepatitis B surface antigen, surface antibody and core antibody.

Positive tests for hepatitis B surface antibody and core antibody indicate the presence of immunity to hepatitis B, and another cause for elevated aminotransferase levels should be sought.

A positive hepatitis B surface antigen indicates hepatitis B infection. Viral replication can be assessed by determining hepatitis B e antigen status. Patients who are hepatitis B e antigen positive have high levels of replicating virus. When hepatitis B e antigen is negative but ALT

Table 3. Additional tests to clarify the cause of abnormal liver tests

Hepatitis C antibody in serum	Presence suggests chronic hepatitis C infection
Hepatitis B surface antigen and e antigen	Hepatitis B surface antigen suggests chronic hepatitis B infection; hepatitis B e antigen suggests active viral replication
Serum ferritin and transferrin saturation	Iron overload suggests haemochromatosis
Antimitochondrial antibodies	Detected in primary biliary cirrhosis
Antinuclear antibodies, anti-smooth muscle antibodies	Detected in autoimmune hepatitis
Serum ceruloplasmin	Decreased in Wilson's disease
Serum alpha-1-antitrypsin	Decreased in alpha-1-antitrypsin deficiency

Table 4. Classes of medications commonly causing abnormal liver tests

- Antibiotics (e.g. amoxycillin–clavulanate, flucloxacillin, minocycline)
- Antipsychotics (e.g. chlorpromazine)
- Antituberculous drugs
- Antiepileptic drugs (e.g. carbamazepine, phenytoin)
- Lipid lowering medications
- Nonsteroidal anti-inflammatory drugs (e.g. ketoprofen, naproxen sodium, diclofenac sodium)
- Oestrogens (e.g. oral contraceptive pill)

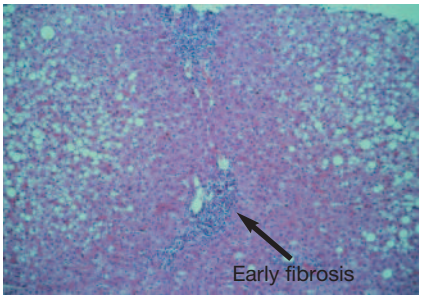


Figure 2. Histological changes seen in chronic hepatitis C, in particular early fibrosis.

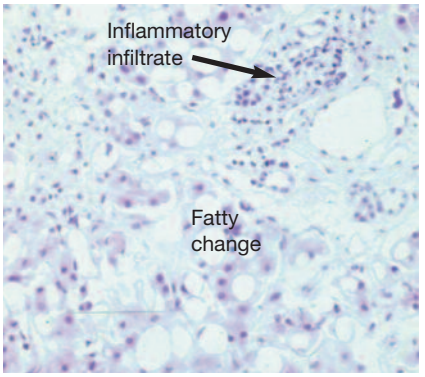


Figure 3. Inflammatory infiltrate and fatty change seen on liver biopsy in nonalcoholic steatohepatitis.

levels are paradoxically raised, specialist assessment should be sought because the patient may be infected with the precore mutant form of hepatitis B virus or have another cause for liver injury. The presence of the precore mutant form can be confirmed by determining serum hepatitis B virus DNA levels. Those infected with precore mutant hepatitis B virus often run a more aggressive course.

Patients with chronic hepatitis B have an approximately 30% lifetime risk of developing hepatitis B-related complications, including hepatocellular carcinoma and liver failure. With the availability of potent antiviral drugs (such as lamivudine) for the treatment of chronic hepatitis B, any patient who is positive for both surface and e antigens and has an elevated ALT (especially if >100 U/L) should be considered for specialist assessment, liver biopsy and treatment. Likewise, patients with precore mutant hepatitis B virus infection and elevated ALT should be considered for antiviral therapy.

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease is the commonest cause of liver test abnormalities in Australia, affecting 20% of obese and 3% of lean individuals. The two conditions of hepatic steatosis and nonalcoholic steatohepatitis (NASH) can clinically manifest as mild elevations in serum aminotransferase levels (usually less than four times the normal value). Patients with NASH usually have an AST:ALT ratio that is less than 1, unless cirrhosis intervenes, in which case the ratio exceeds 1.

Ultrasonography is a useful adjunct in the assessment of a patient with suspected NASH. Fatty involvement of the liver appears on ultrasound as a hyperechoic liver, but such an appearance is nonspecific, being indistinguishable from that due to hepatic iron deposition or fibrosis.

Hepatic steatosis and NASH are found in association with disorders of insulin resistance such as type 2 diabetes, obesity (especially central) and hyperlipidaemia (hypertriglyceridaemia and/or low HDL). The distinction between steatosis and NASH is made on liver biopsy, with the former showing bland fatty infiltration (steatosis) and the latter showing steatosis as well as inflammation and variable fibrosis (Figure 3).

Distinguishing both conditions is important because hepatic steatosis is a benign, non- or slowly progressive condition. In our series of patients at Westmead Hospital, female gender, diabetes mellitus and hyperinsulinaemia were identified as independent predictors of severe fibrosis in patients with NASH. Serious consideration has to be given to implementing lifestyle modifications (regular exercise and a low-fat weight reduction diet) early in this group of patients, as well as careful monitoring and stringent control of underlying disorders of insulin resistance.

Haemochromatosis

Hereditary haemochromatosis is a common genetic disorder (1 in 200) that can present with abnormal liver tests. Widely available and cost effective screening tests include measuring serum ferritin and fasting transferrin saturation (serum iron divided by total iron binding capacity). A fasting transferrin saturation of greater than 45% is suggestive of haemochromatosis. Serum ferritin is less specific because it is an acute phase reactant and is often raised in conditions such as alcoholic and nonalcoholic steatohepatitis.

Genetic testing can now be performed to identify the mutations C282Y and H63D in the haemochromatosis (*HFE*) gene. A liver biopsy is necessary (to assess the degree of fibrosis) if iron overload is present on iron studies but no *HFE* mutation is found on genetic testing, or if a patient with the *HFE* mutation is older than 40 years of age, or has a serum ferritin >1000 µg/L, or has hepatomegaly or an abnormal AST. Family screening is mandatory in all first-degree relatives. If the individual has an elevated transferrin saturation and is a C282Y homozygote, or a compound C282Y/H63D heterozygote, then a liver biopsy can be avoided if the patient is under the age of 40 years and the serum aminotransferase levels are normal.

Autoimmune hepatitis

This diagnosis should be considered when a young woman presents with a hepatocellular pattern of elevated liver enzymes and raised globulins that on serum immunoelectrophoresis consist predominantly of IgG. Autoimmune markers for this condition include antinuclear antibodies and antibodies against smooth muscle (SMA) and liver-kidney microsomes (LKM). A liver biopsy is essential in confirming the diagnosis. Untreated, autoimmune hepatitis can rapidly progress to cirrhosis and liver failure. Thus, new patients must be referred early for assessment and therapy.

Wilson's disease

Wilson's disease is a rare genetic disorder in which copper accumulates in the liver and brain in excess of normal metabolic needs. The underlying defect is a reduction in the biliary excretion of copper. All young patients (<40 years) with new liver test abnormalities should be evaluated for Wilson's disease by way of a serum ceruloplasmin level. Serum ceruloplasmin levels are reduced in 85% of affected individuals. Ophthalmological assessment looking for Kayser–Fleischer rings is also recommended.

A 24-hour urine collection to quantify copper excretion may be useful, particularly if a clinician strongly suspects Wilson's disease in a patient with absent Kayser–Fleischer rings and a normal serum ceruloplasmin level. Liver biopsy is recommended to measure hepatic copper levels and ascertain the degree of hepatic fibrosis.

Alpha-1-antitrypsin deficiency

This is an uncommon cause for abnormal liver tests in adults. Decreased levels of alpha-1-antitrypsin can be detected by direct measurement of serum levels. The diagnosis is established by phenotypic determination.

Elevated alkaline phosphatase levels

Liver and bone are two sources of ALP. Women in their third trimester of pregnancy have raised ALP levels because of the passage of placental ALP into the maternal circulation. Serum levels vary with age and gender. Adolescents can have serum ALP levels twice those of healthy adults as a result of bone ALP leaking in to blood. Serum ALP gradually increases from the age of 40 up to the age 65, especially in women.

The initial step in evaluating an elevated ALP level is to consider it in tandem with the serum GGT. A raised ALP in the presence of an elevated GGT suggests that the ALP is of liver origin. If liver enzymes demonstrate a cholestatic pattern, chronic cholestatic and infiltrative liver disorders should be considered. Cholestatic disorders include obstruction of bile ducts, drug induced cholestasis, primary biliary cirrhosis and primary sclerosing cholangitis (Table 2).

In evaluating cholestatic liver abnormalities that are not considered to be drug related, ultrasonography is recommended to assess the hepatic parenchyma and bile ducts. If biliary dilatation or choledocholithiasis is found, diagnostic and therapeutic endoscopic retrograde cholangiopancreatography should be undertaken. If no obstructive cause is identified on ultrasonography, the patient will require referral to exclude rare conditions such as primary biliary cirrhosis, primary sclerosing cholangitis

or sarcoidosis. Serological testing for antimitochondrial antibodies is used to screen for primary biliary cirrhosis. If a patient tests positive, the diagnosis is confirmed by liver biopsy.

Elevated gamma glutamyltransferase levels

Gamma glutamyltransferase is found in hepatocytes and biliary epithelial cells. Raised levels of GGT can be found in a wide variety of clinical conditions, including pancreatic disease, myocardial infarction, renal failure, chronic obstructive airways disease and diabetes. Patients taking phenytoin and barbiturates commonly have an elevated GGT.

The sensitivity of an elevated GGT for detecting alcohol ingestion ranges from 52 to 94%. Its lack of specificity makes it unreliable for this purpose. Measurement of serum GGT is best used as an adjunct in interpreting the pattern of elevations of the other liver tests.

Hyperbilirubinaemia

It is important to note that hyperbilirubinaemia may be present in association with both hepatocellular (e.g. viral hepatitis) and cholestatic (e.g. bile duct obstruction) patterns of liver test abnormalities.

When patients with haemolysis or overt liver disease have been excluded, there remain those with familial abnormalities of bilirubin metabolism. The commonest is Gilbert's syndrome, which is a benign, mild, unconjugated hyperbilirubinaemia that is not due to haemolysis and is seen with normal synthetic liver function and histology. It affects up to 5% of the population and has an autosomal dominant inheritance. Jaundice is mild and intermittent, with exacerbations following infection or fasting, and may be associated with malaise, nausea and right upper quadrant discomfort. Gilbert's syndrome has an excellent prognosis, with normal lifetime expectancy and normal risk for life insurance.

Conclusion

In summary, the cause of liver test abnormalities in most cases can be elicited by a detailed history and examination. However, any persistent elevation of liver test results warrants further investigation, such as abdominal imaging, serological testing or referral to a gastroenterologist. Assessing the pattern and degree of liver test abnormalities may provide clues to the underlying cause. MT

Reference

1. Chitturi S, Farrell GC. Herbal hepatotoxicity: an expanding but poorly defined problem. J Gastroenterol Hepatol 2000; 15: 1093-1099.

Further reading

1. Pratt DS, Kaplan MM. Laboratory tests. In: Schiff ER, Sorrell MF, Madrey WC, eds. Schiff's diseases of the liver. 8th ed. Vol 1. Philadelphia: Lippincott-Raven, 1999: 205.
2. Chitturi S, Fung C, Farrell GC, Samarasinge D, Lin R, George J. Biochemical predictors of advanced hepatic fibosis in NASH. J Gastroenterol Hepatol 2000; 15 Suppl: J17.
3. Farrell GC, Weltman M. Drug-induced liver disease. In: Gitnick Q, ed. Current hepatology. Vol 16. St Louis : Mosby, 1996: 143.
4. Farrell GC. Chronic viral hepatitis. Med J Aust 1998; 168: 619-626.
5. Bacon BR, Powell LW, Adams PC, Kresina TF, Hoofflagle JH. Molecular medicine and haemochromatosis: at the crossroads. Gastroenterology 1999 ; 116: 193-207.
6. Powell L, Yapp T, Monk C, Watson K. Haemochromatosis : a guide for health care providers. Australian Gastroenterology Institute Statement. Mod Med Aust 1999; 42(11): 51-59.
7. Czaja A. Autoimmune hepatitis: evolving concepts and treatment strategies. Dig Dis Sci 1995; 40: 435-456.
8. Benichou C. Criteria for drug-induced liver disorders. Report of an International Concensus Meeting. J Hepatol 1990; 11: 272.
9. Farrell GC. Hepatitis C, other liver disorders and liver health: a practical guide. Sydney: MacLennan and Petty, 2002.