Liver function tests

Introduction

The term 'liver function tests', used typically to describe the liver profile on a laboratory request form, is in fact a misnomer as several of the tests involved are not tests of liver function, but of hepatic enzyme release either as a result of induction or damage. This article will refer to liver profile tests except when specifically referring to liver function. As the body's hepatic reserve is considerable, liver function generally only begins to decline in the face of advanced or severe acute disease, and the liver profile is used to detect abnormalities that may indicate disease. They rarely diagnose the cause of the liver disease in question but can throw light on the category of disease, i.e. obstructive or hepatic.

Several interpretative pitfalls exist, first because several of the existing tests are not specific to the liver (Aranda-Michel and Sherman, 1998; Minuk, 1998), and second because liver profiles can be normal in advanced disease (Mofrad et al, 2003; Keating and Plosker, 2005) and conversely, not all, particularly minor, abnormalities are clinically significant (Bosma et al, 1995).

This article examines the different tests available, their overall interpretation, and the means of further diagnosis in liver disease.

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What laboratory liver function tests are available?

Table 1 does not give an exhaustive list of those tests used, but covers the majority of tests currently or recently used.

Bilirubin is produced mostly from haem metabolism and is conjugated in the liver before being excreted in bile. Increased bilirubin levels may therefore be conjugated as a result of a conjugation defect in the liver (e.g. biliary obstruction, hepatocellular failure) or unconjugated (e.g. excess production in haemolysis saturating the conjugation system, or congenital defect in Gilbert's syndrome; Smellie et al, 2006).

Aspartate aminotransferase (AST) is not specific to the liver and, although used by some as a pointer towards the cause of disease in some situations (e.g. alcoholic liver disease, when it is raised proportionally more than alanine aminotransferase; ALT), is of limited routine use.

ALT is relatively specific to the liver and is the primary biochemical marker of hepatocellular injury.

Alkaline phosphatase is primarily a canalicular enzyme which rises in obstruction, although it exists as liver, bone, intestinal and placental isoenzymes. In practice the main issue which arises is determining whether an isolated rise is of hepatic or bone origin. Two different types of measurement methods are currently used which have different reference ranges and are therefore a potential source of confusion.

Gamma glutamyltransferase (γGT) is also a canalicular enzyme which rises in obstruction and is induced by several drugs including alcohol. It is wrongly considered by many to be a marker of alcohol abuse for which it is neither sensitive nor specific. Its main purpose is as a secondary cause to identify the likely cause of a raised alkaline phosphatase level of uncertain origin (Minuk, 1998; Pratt and Kaplan, 2000).

Table 1. Common liver profile tests and examples of liver function tests with indication of what the test does and relative specificity for the liver

Liver profile test	Current use	Test of	Liver specificity and differential diagnosis
Bilirubin	Most/all liver profiles	Bilirubin production and removal Can be a test of liver function	Average. Main differential is haemolysis (unconjugated)
Aspartate aminotransferase	Some liver profiles	Cell enzyme release	Poor, released by many tissues
Alanine aminotransferase	Most/all liver profiles	Cell enzyme release	Good, limited quantitative utility
Alkaline phosphatase	Most/all liver profiles	Cell enzyme release	Average. (Main differential is bone) Gamma glutamyltransferase may help
Gamma glutamyltransferase	Some liver profiles	Cell enzyme release	Good but extremely sensitive. Poor quantitative utility
Total protein	Most/all liver profiles	Hepatic synthesis	Poor. Included mostly to detect possible myeloma
Albumin	Most/all liver profiles	Hepatic synthesis Can be used as test of function	Limited. Differentials of protein loss and haemodilution
Globulins	Most/all liver profiles	Hepatic synthesis	Poor, often reflects chronic systemic disease
Tests of liver function			
Ammonia	Specific function test	Hepatic metabolism (urea cycle)	Good
Prothrombin ratio or INR	Separate function test	Simple test of hepatic synthesis	Relatively good, quantitative*. Main differentials often apparent
Aminopyrene breath test	Specific function test	Hepatic metabolism (microsomal)	Good, quantitative

INR = international normalized ratio. *assuming patient not on warfarin, and not suffering from other coagulopathy, e.g. disseminated intravascular coagulation, or severe vitamin K deficiency (these are usually clinically apparent)

Total protein has been included historically in the liver profile. While the main circulating proteins are indeed produced by the liver, total protein reflects more the other states which stimulate production of the major proteins such as inflammation.

Albumin is a test of liver function, although low albumin can also reflect haemodilution (e.g. secondary hyperaldosteronism) or increased albumin losses (e.g. nephrosis). As advanced liver disease is also associated with secondary hyperaldosteronism the proportionate contributions of these two to a low albumin result can be difficult to assess in this situation.

Globulins (not to be confused with measurement of the individual immunoglobulin classes A, G and M) are those non-albumin proteins in the blood (i.e. total protein level – albumin level), and are made up mostly of immunoglobulins. Raised globulin levels therefore frequently reflect chronic inflammation or plasma cell dyscrasia such as myeloma rather than hepatic disease.

The prothrombin ratio or its counterpart the international normalized ratio (INR) is a test of liver function (production of vitamin K-dependant coagulation factors) and is an early measure of hepatic dysfunction. This is not part of a biochemical liver profile.

Ammonia (NH3) is a marker of hepatic nitrogen metabolism, used particularly in the investigation of the cause of encephalopathy and in the initial investigation of suspected inborn errors of the urea cycle.

The aminopyrene breath test is an example of a specific quantitative test of liver function, not used for routine patient assessment, but to establish the degree of liver dysfunction usually in established liver disease.

How do I interpret abnormalities?

The cause of acute or chronic liver disease can be established from the clinical history, examination and relatively straightforward investigations in a large majority of cases. The clinical history must not omit a detailed drug history including over the counter health preparations, and excluding the possibility of poisoning with paracetamol, ethylene glycol and other potential hepatotoxic agents depending on the clinical presentation.

Although referral recommendations vary, most patients with clinical and laboratory evidence of liver disease are subsequently referred to specialist services, although the underlying cause can usually be established first from the set of investigations in *Table 2*.

Laboratory investigation of liver disease begins with identification of the type of abnormality present:

- Hepatic, characterized by a rise in transaminases (ALT)
- Obstructive, characterized by a rise in alkaline phosphatase (and γGT if necessary for confirmation) and later in conjugated bilirubin.

As hepatic changes progress to structural liver damage obstructive changes can then occur and, conversely, obstructive changes result in pooling of bile within the liver, causing secondary hepatic changes (ascending cholangitis). Liver profile patterns are often therefore mixed, although in most situations the predominant abnormality suggests the mechanism of origin.

Large rises in enzymes (typically defined as more than five times the upper limit of normal) are usually accompanied by other liver test changes forming a characteristic pattern and suggesting a possible origin.

What are the main tests used to investigate liver disease?

A list of candidate investigations for the most common causes of chronic liver dis-

Table 2. Aetiological investigations in asymptomatic patients with chronic liver profile abnormalities. Level 1: suggested first investigation set; level 2: if no diagnosis obtained after level 1 before referral for consideration for diagnostic liver biopsy

Test		Abnormality	Interpretation
Level 1	Plasma glucose, lipids	Hyperglycaemia	Identifies probable contribution from non-alcoholic fatty liver disease hypertriglyceridaemia
	Full blood count	Macrocytosis	Suggests alcohol excess if gamma glutamyltransferase also elevated
		Thrombocytopenia	Possible hypersplenism (portal hypertension)
	Autoantibodies	AMA positive, IgM	Probable primary biliary cirrhosis
		ASMA/ANA positive	Strongly suggestive of autoimmune hepatitis
	Ferritin, transferrin saturation	Elevated	Possible haemochromatosis, consider gene mutation testing
	Hepatitis B surface antigen	Positive	Implies chronic infection
	Hepatitis C antibody	Positive	Suggests chronic infection
Level 2	Liver ultrasound	Mass/dilated ducts	Tumour or stones
		Echobright fatty infiltration	Non-alcoholic fatty liver disease or alcoholic fatty liver disease
	Anti-endomysial antibodies	Positive	Suggests coeliac disease
	Alpha-1-antitrypsin level	Low	Suggests deficiency. Phenotype required. (PiZZ or PiM alleles implicated)
	Others, e.g. caeruloplasmin, urine copper as dictated by clinical context	Low	Wilson's disease

AMA = antimitochondrial antibody; ASMA = anti-smooth muscle antibody; ANA = antinuclear antibody. Adapted from Limbi and Hyde (2003)

Table 3. Findings on liver biopsy for unexplained abnormal liver enzyme elevation in 354 patients

Final diagnosis	No. (%)
Non-alcoholic steatohepatitis	120 (34)
Non-alcoholic fatty liver disease	115 (32)
Cryptogenic hepatitis	32 (9)
Drug-related damage	27 (7.6)
Normal liver	21 (5.9)
Alcohol	10 (2.8)
Autoimmune hepatitis	7 (1.9)
Granuloma or sarcoid	6 (1.7)
Primary biliary cirrhosis	5 (1.4)
Primary sclerosing cholangitis	4 (1.1)
Haemochromatosis	3 (0.9)
Secondary biliary cirrhosis	2 (0.6)
Amyloid	1 (0.3)
Glycogen storage disease	1 (0.3)

From Skelly et al (2001)

ease is shown in *Table 2*. This is non-exhaustive but includes causes making up the great majority of cases presenting to primary and secondary care services (*Table 3*). In everyday practice the majority of cases involve non-alcoholic steatohepatitis or other non-alcoholic fatty liver disease with or without hypertriglyceridaemia, diabetes, the metabolic syndrome and a greater or lesser additional contribution from alcoholic liver disease. One of the main diagnostic challenges is identifying liver disease resulting from other causes.

In most situations onward referral would be recommended if these investigations fail to reveal a cause, as the clinical investigation of rarer causes such as glycogen storage disease, glycolipidoses or other adult or childhood presenting inborn errors of metabolism is probably best performed in specialist hands.

Conclusions

The tests included in the liver profile (or 'LFT') are not all specific for the liver and do not in themselves reveal the cause of liver disease. They can, however, point towards a disease mechanism, notably obstructive and hepatic, although many abnormalities are mixed. Fatty liver disease is the commonest cause of asymptomatic liver profile abnormalities, but it is important to identify other, potentially treatable conditions. A simple range of subsequent laboratory tests will reveal the cause in the majority of cases. The Association of Clinical Biochemists is currently working to offer a recommended standard set of tests to include in this profile, as historically laboratories have developed their own profiles for local use and some of the tests used previously may now be redundant.

A set of researched answers to frequently asked questions on liver profile abnormalities can be found on www.bettertesting.org.uk, set up by the author in conjunction with the Sowerby Centre for Health Informatics, Newcastle. BJHM

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KEY POINTS

- Several 'liver function tests' are actually tests of enzyme release from the liver.
- Isolated liver profile abnormalities are common and often non-specific findings.
- The commonest cause of isolated raised transaminase levels is fatty liver.
- Persistent asymptomatic abnormalities over twice the upper reference limit justify further investigation.
- Early referral is appropriate if any signs of liver disease are present.

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