Investigation of jaundice

Diarmaid D Houlihan
Matthew J Armstrong
Philip N Newsome

Abstract

Jaundice is an important clinical sign reflecting the accumulation of bilirubin in blood. It is frequently associated with significant underlying disease. It can result from increased bilirubin production (due to haemolysis); inability of the liver to take up and/or conjugate bilirubin (in Gilbert's syndrome or parenchymal liver disease); or failure to excrete bilirubin into biliary canaliculi and/or into the biliary tree (when the bile ducts are obstructed). Appropriate investigation of a jaundiced patient starts with a detailed history that will often give vital clues to the diagnosis. Clinical examination should look for the presence of stigmata of chronic liver disease to determine the possible chronicity of liver injury. Liver function tests (LFTs) include a variety of different biochemical measurements reflecting hepatocyte and cholangiocyte injury, as well as liver synthetic function. Accurate interpretation of the different patterns (hepatitic versus cholestatic) of LFT derangement allows for the efficient choice of further investigations. This review will detail the steps involved in bilirubin metabolism, the causes of jaundice and subsequently the appropriate investigation of a patient with jaundice.

Keywords biliary obstruction; cirrhosis; conjugated and unconjugated bilirubin; haemolytic anaemia; hepatitis; hyperbilirubinaemia; jaundice; liver injury

What's new?

- There is an expanding role for endoscopic ultrasound (EUS) in the investigation of patients with jaundice
- The sensitivity and specificity of EUS for the diagnosis of choledocholithiasis is at least equivalent to that of magnetic resonance cholangiopancreatography
- EUS has emerged as a useful additional test for the diagnosis and staging of pancreatic cancer
- EUS allows for the biopsy of suspicious lesions that would traditionally require percutaneous biopsy

Introduction

Jaundice describes yellow discolouration of the skin, mucous membranes and sclera, and becomes clinically apparent when the serum bilirubin is more than twice the upper limit of normal (>34 μmol/litre). Jaundice is often the first or only sign of hepatobiliary or pancreatic disease, and a systematic approach is required to identify the underlying cause and commence appropriate therapy. Understanding the physiological steps involved in the metabolism and clearance of bilirubin is vital to the effective investigation of a patient presenting with jaundice.

The majority of bilirubin (80%) is formed following the breakdown of haem present in the haemoglobin of red blood cells. The typical life span of a red blood cell is 120 days after which it is destroyed in the spleen (reticuloendothelial system). The released haem molecule is converted to biliverdin and then water-insoluble bilirubin via a series of enzymatic reactions. Bilirubin circulates, avidly bound to albumin, from which it is released in the liver sinusoids and actively taken up by hepatocytes, while albumin remains in the circulation (Figure 1).

Within the hepatocyte, bilirubin is conjugated to glucuronic acid by the enzyme UDP-glucuronosyltransferase, rendering it water-soluble so that it can be excreted into bile. The majority (98%) of bilirubin entering the gut is not absorbed by the small intestinal epithelium. It is degraded by bacterial enzymes in the colon to form urobilinogens (stercobilinogen and urobilinogen) that are excreted in the stool and urine. Under certain pathological conditions in which conjugated bilirubin cannot enter the gut, such as obstructive jaundice, 50–90% is excreted by the kidney.

Type of jaundice – conjugated or unconjugated hyperbilirubinaemia?

Discovering whether accumulated serum bilirubin is conjugated or not helps to identify the underlying cause of jaundice and is therefore an important first step. The presence of bile in the urine indicates jaundice due to conjugated hyperbilirubinaemia. A more quantitative analysis can be obtained by measurement of conjugated (direct) and unconjugated (indirect) bilirubin in the blood.

Unconjugated hyperbilirubinaemia

Elevation of a predominantly unconjugated bilirubin can result from overproduction of bilirubin, impaired bilirubin uptake by the liver, or abnormalities of bilirubin conjugation (Figure 1). A detailed list of the causes of unconjugated hyperbilirubinaemia is given in Table 1.

Conjugated hyperbilirubinaemia

Causes of conjugated hyperbilirubinaemia can be divided into hepatocellular injury, intrahepatic cholestasis, and biliary

Diarmaid D Houlihan *MB BSc MRCP is an MRC clinical research fellow currently working in the centre for liver research, NIHR Biomedical Research Unit, University of Birmingham, UK. He is a specialist registrar in hepatology. His research interest is the potential therapeutic effects of mesenchymal stem cells in liver injury. Conflicts of interest: none.*

Matthew J Armstrong *MB BSc MRCP is a Wellcome Trust clinical research fellow currently working in the centre for liver research, NIHR Biomedical Research Unit, University of Birmingham, UK. He is a specialist registrar in hepatology. His research interest is therapy of non-alcoholic fatty liver disease. Conflicts of interest: none.*

Philip N Newsome *PhD FRCPE is a senior lecturer/consultant at the Liver Unit in Birmingham and is the clinical lead for metabolic liver disease. He is the Clinical Director of the Birmingham University Stem Cell Centre, UK. Conflicts of interest: none.*

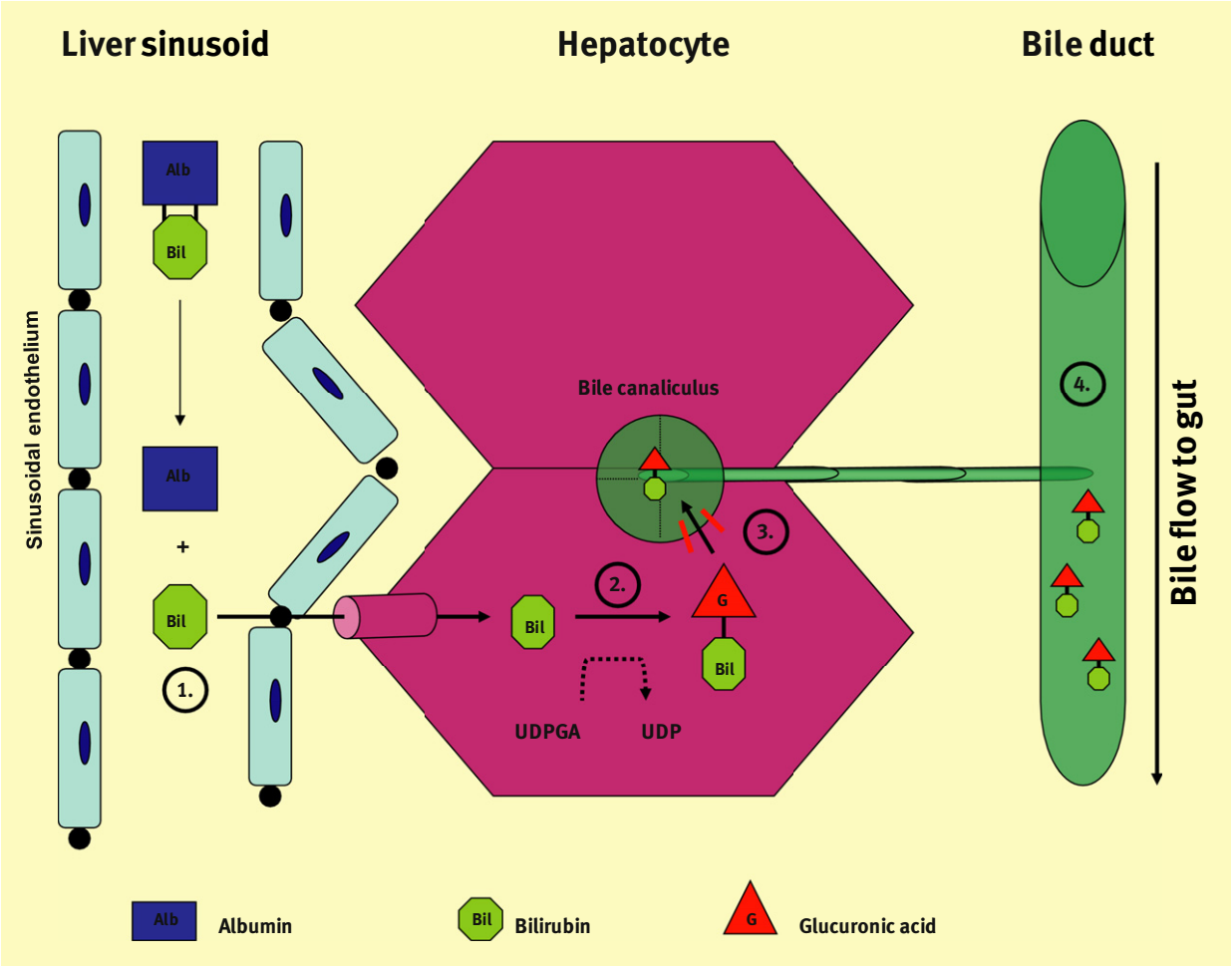

Figure 1 The key steps involved in bilirubin metabolism. Unconjugated bilirubin from red blood cell breakdown travels to the liver bound to albumin. Bilirubin is taken into the hepatocyte by active transport. Bilirubin is then conjugated to glucuronides by glucuronyl transferase making it water-soluble. Conjugated bilirubin is then excreted into the bile and hence into the gut. Causes of jaundice include: 1. haemolysis or failure of hepatic bilirubin uptake 2. impaired bilirubin conjugation (reduced or absent glucuronyl transferase activity) 3. impairment of bilirubin excretion into the biliary canaliculus 4. blockage to biliary drainage.

obstruction. A list of the disease states that cause conjugated hyperbilirubinaemia is given in Table 2. As well as the common causes, such as cirrhosis and acute liver injury, elevated conjugated bilirubin can also occur in rare inherited diseases such as Dubin–Johnson syndrome, Rotor syndrome, progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis, and low phospholipid-associated cholelithiasis.

Investigations

History

The diagnostic approach to the jaundiced patient begins with a careful history and physical examination. The physician should first inquire about:

- symptoms, such as itch, loss of appetite, weight loss, pale stools, dark urine, fever and abdominal pain

Causes of unconjugated hyperbilirubinaemia

Increased bilirubin production	Impaired hepatic bilirubin uptake	Impaired bilirubin conjugation
Extravascular haemolysis	Hepatic failure	Gilbert's syndrome
Haematoma	Portosystemic shunts	Criglar–Najjar syndrome
Intravascular haemolysis (haemolytic anaemia)	Medications (rifampicin and probenecid)	Neonates
Dyserythropoiesis (hereditary spherocytosis)	Congestive cardiac failure	Advanced cirrhosis
		Hyperthyroidism
		Medications (ethinyl oestradiol)

Table 1