Jaundice: applying lessons from physiology

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Abstract

Jaundice is a common presentation in medical and surgical gastroenterology practice. Knowledge of the physiology of bilirubin metabolism will help the clinician to understand the mechanisms of development of jaundice. This along with clinical evaluation, laboratory investigation and non-invasive imaging will help when making a firm diagnosis. Further management may require advanced imaging and/or invasive techniques, which should be chosen in the light of the given clinical scenario based on the risk-benefit ratio, local availability and expertise.

Keywords Bilirubin; diagnosis; hyperbilirubinemia; jaundice

Introduction

Jaundice is derived from the French word "jaune" meaning yellow discolouration. It is the most common sign of liver disease. It is characterised by yellow discolouration of the skin and mucous membranes due to abnormal increase in the serum bilirubin concentration. Tissue deposition of bilirubin occurs only in the presence of serum hyperbilirubinemia and is usually a sign of liver disease or less commonly haemolytic disorder. Clinical examination usually reveals the degree of hyperbilirubinemia. The earliest place to manifest jaundice is the sclera due to the high elastin in the scleral tissue and the affinity of bilirubin to it. The presence of scleral icterus indicates a serum bilirubin of at least 50 μmol/L. Greenish tinge to icterus indicates longstanding jaundice and is due to oxidation of bilirubin to biliverdin.

The other causes for yellowing of the skin are carotenoderma, which is due to excess consumption of carotene-containing foods such as carrots and leafy vegetables, wherein the sclera is spared and the yellow pigmentation is concentrated over the palms, soles, forehead, and nasolabial creases. Drugs such as quinacrine and exposure to phenols also cause yellow discolouration. Another indicator of jaundice is dark urine or tea or cola coloured urine, which the patients commonly describe. Jaundice has various causes and attempts to classify jaundice dates back to the time of Hippocrates. By the time of William Osler, distinctions were made between obstructive and non-obstructive jaundice. In the latter part of the 20th century with a better understanding of the bilirubin metabolism, progress in imaging technology and sophisticated biochemical methods, the exact cause of jaundice could be elucidated. Hyperbilirubinemia occurs when the balance between production and clearance is altered and thus a logical evaluation of a jaundiced patient requires the understanding of bilirubin production and metabolism.

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Bilirubin metabolism (Figure 1)

Sources of bilirubin

Bilirubin, a tetrapyrrole pigment moiety, is a breakdown product of haem (Ferriprotoporphyrin IX). In a normal healthy person daily bilirubin production averages about 0.5 mmol (250–300 mg). About 80% of this bilirubin is derived from breakdown of haemoglobin from senescent red blood cells (RBCs) in the reticuloendothelial system, 15% from ineffective erythropoiesis in the marrow and 5% from turnover of haemoproteins such as myoglobin, catalases and cytochromes enzyme system elsewhere in the body.

Production of bilirubin

The production of bilirubin takes place in the reticuloendothelial system in a two-step process. First is oxidation of the haem by haem oxygenase involving breaking open of the alpha bridge resulting in the formation of biliverdin. Second step is reduction of this green pigment by biliverdin reductase to colourless bilirubin.

Plasma transport

The bilirubin so formed in the reticuloendothelial cells is virtually insoluble in water and potentially toxic. To be transported in blood the bilirubin binds reversibly and non-covalently with albumin.

Hepatic uptake

Unconjugated bilirubin tightly bound to albumin is transported to the liver where the bilirubin but not the albumin is taken up across the basolateral membrane of the hepatocytes by a carrier mediated transport process possibly via a member of the organic anion transporter (OATP) family.[1] Within the cytosol, two cytosolic binding proteins ligandins Y and Z transport the bilirubin to the smooth endoplasmic reticulum of the hepatocyte for conjugation with glucuronic acid and also to prevents efflux of bilirubin back in to plasma.

Hepatic conjugation

In the presence of the co-substrate uridine diphosphate (UDP), the enzyme uridine diphosphoglucoronyl transferase (UDP-GT) medicates conjugation of the hydrophobic bilirubin to hydrophilic bilirubin monoglucuronide and diglucuronide conjugates that are suitable for excretion. This enzyme is encoded by the UDP-GT gene on chromosome 2. Mutations in the gene form the basis of the congenital unconjugated hyperbilirubinemias. The UDP-GT activity is well maintained in both acute and chronic hepatocellular damage and even increased in cholestasis by gene up regulation.[2]

Biliary excretion

These then diffuse from the endoplasmic reticulum towards the apical cell membrane or the canalicular membrane to be excreted into bile canaliculi by an ATP dependent export pump belonging

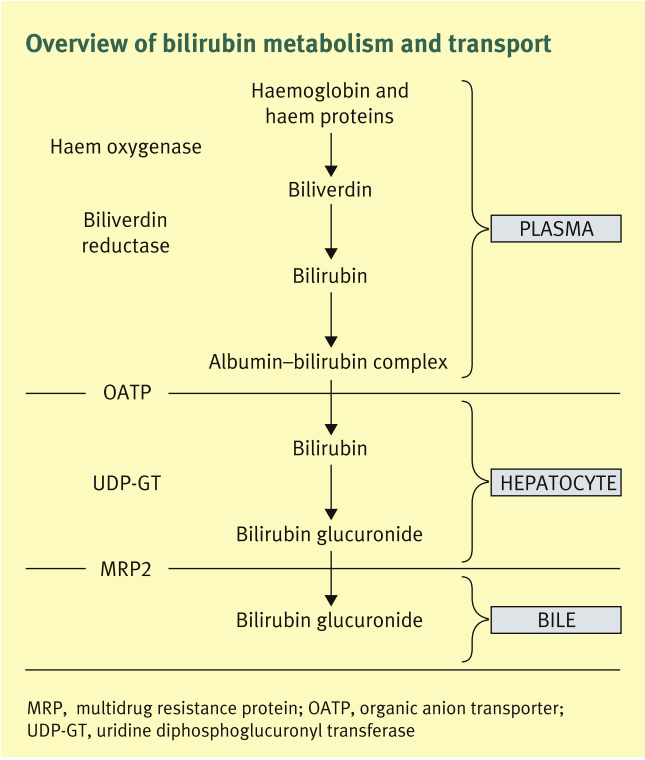

Figure 1

to the multidrug resistance protein 2 (MRP2).[3] This forms the rate-limiting step in the synthesis in bilirubin metabolism. This step is affected in both acute and chronic hepatocellular injury thus explaining the rise in predominantly conjugated bilirubin in such cases. Small amounts of conjugated bilirubin are secreted across the sinusoidal membrane by MRP3 directly into blood stream, which undergoes renal excretion. Normally 80–85% of the bile is made of bilirubin diglucuronide and 15–19% of bilirubin monoglucuronide and remaining made of traces of unconjugated bilirubin. The conjugated bilirubin excreted into bile drains into duodenum and passes unchanged in the proximal small bowel until it reaches the distal small bowel and colon wherein it is hydrolysed by the intestinal bacterial betaglucuronidase to unconjugated bilirubin. This is then further reduced by the gut flora to colourless urobilinogen. Between 80% and 90% of this is excreted in the faeces either unchanged or oxidized to urobilin or stercobilin, which imparts the natural colour to the stools. The remaining 10–20% of the urobilinogen is passively absorbed and circulated in the enterohepatic circulation for re-conjugation and to be excreted in bile. A trace of this absorbed in the enterohepatic circulation escapes hepatic uptake into the systemic circulation and filtered across the glomerulus to be excreted in the urine.

Measurement of bilirubin

Serum bilirubin is measured using a variation of the original Van den Bergh colorimetric reaction. The indirect and direct refers to the total and conjugated bilirubin levels respectively. With the Van den Bergh method the normal total serum bilirubin concentration is 17 μmol/L (<1 mg/dl). Up to 30% (i.e. 5.1 mol/L [0.3 mg/dl]) is in the conjugated form. Increased understanding of the bilirubin metabolism and sophisticated methods of measurements of bilirubin have led to the belief that in jaundiced patients with hepatobiliary disease, the bilirubin monoglucuronide fraction is higher. Unconjugated bilirubin is bound to albumin and hence not filtered in the glomerulus but conjugated bilirubin is, and almost all of it is reabsorbed by the proximal tubules and very small traces are excreted in urine. Thus presence of bilirubinuria is a suggestion of liver disease. However in prolonged cholestatic jaundice the conjugated bilirubin fraction in serum covalently binds to albumin, which explains the reason why the bilirubin levels declines more slowly than clinical recovery due to longer half-life of albumin.

Disorders of bilirubin metabolism

Hyperbilirubinemias can result from any defects in the steps of bilirubin metabolism mentioned earlier:

- overproduction
- impaired uptake and conjugation lead to unconjugated/indirect hyperbilirubinemia and
- impaired excretion of bilirubin from damaged hepatocytes or bile ducts leads to direct/conjugated hyperbilirubinemia.

Overproduction of bilirubin

Haemolytic disorders either inherited or acquired leading to excessive haem production cause hyperbilirubinemia. In these conditions, the serum bilirubin rarely exceeds 86 μmol/L (5 mg/dL). Generally these groups of patients have elevated serum haptoglobulin and reticulocyte counts and there is no alteration in liver enzymes (Table 1). Accelerated haemolysis especially in inherited conditions is associated with formation of pigment gallstones that may obstruct biliary tree and lead to conjugated hyperbilirubinemia with elevated liver enzymes.

Impaired uptake and conjugation

Certain drugs like rifampicin, probenecid and protease inhibitors like indinavir cause unconjugated hyperbilirubinemia by reducing the hepatic uptake.[4] Rare inherited syndromes such as Crigler Najjar syndromes I and II and Gilbert's syndrome are caused by dysfunctional or absence of UDPG enzyme activity. Crigler Najjar I is very rare and is characterized by complete absence of the enzyme UDPG leading to neonatal kernicterus and death. Crigler Najjar II is more common and there is reduced activity of the enzyme and patients live to adulthood. Gilbert's syndrome is quite common and is due to reduced enzyme activity and manifests clinically as very mild jaundice especially in times of physiological stress characterized by isolated rise in serum bilirubin (unconjugated fraction) and normal enzymes.

Impaired excretion

Elevated conjugated hyperbilirubinemias occur in two rare syndromes namely Rotor's syndrome, which is due to defective storage of bilirubin in the hepatocytes, and Dubin Johnson's syndrome, which is due to defect in the MRP2 gene.[4] Both these cause asymptomatic jaundice and run a benign course.

When a clinician encounters a patient with jaundice, the basic liver function test can indicate the pattern jaundice (i.e. whether hepatocellular or cholestatic). In hepatocellular conditions (Table 2) there is a disproportionate rise in the cellular enzyme concentration namely the alanine aminotransferase (ALT) and