Jaundice: when and where to look for

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Learning objectives

The purpose of this exhibit is to review the metabolism of bilirubin and the causes of jaundice in the adult population. Pathologies that present with an increase of unconjugated and conjugated bilirubin will be revised, especially emphasizing on obstructive causes. Different cases will be illustrated with US, CT and MR imaging techniques.

Background

BILIRUBIN METABOLISM

Bilirubin is a product of the daily natural destruction of red blood cells in the body. The hemoglobin molecule that is released into the blood by this process splits, with the heme portion undergoing a chemical conversion to bilirubin in the reticuloendothelial system. After bilirubin is released from reticuloendothelial cells, it travels in the blood, bound to albumin and it is known as unconjugated or indirect bilirubin, which is water insoluble. Bilirubin reaches and enters the hepatocytes and will be conjugated to glucuronic acid by the glucuronyl transferase and then be ready for excretion in the form of bile. The process of conjugation makes the bilirubin water soluble, and thus easier to excrete through the kidney. It is then referred to as direct bilirubin. Very small amounts of bilirubin will somehow evade this process and end up in bile as unconjugated bilirubin.

Conjugated bilirubin is not reabsorbed from the intestine, but the small amount of unconjugated bilirubin that appears in the bile is partially reabsorbed. Intestinal bacteria degrades bilirubin into urobilinogen, most of which is absorbed from the intestine and excreted in bile, and a small fraction is excreted in urine.

JAUNDICE

If there is a disruption of this normal metabolism, production or excretion of bilirubin, jaundice may result. Jaundice is a yellow discoloration of the skin, mucous membranes, and the sclerae caused by increased amounts of bilirubin in the blood. Scleral icterus can usually be detected when the serum bilirubin exceeds 3.0 mg/dL. It can be classified in two categories; unconjugated and conjugated hyperbilirubinemia. The first ones are due to an increased rate of hemolysis or defects in bilirubin conjugation and rarely have radiological findings. Conjugated hyperbilirubinemia can be caused by liver cell dysfunction that reduces bilirubin metabolism and excretion, or by obstructive processes at different levels. Liver and biliary diseases are the leading cause of jaundice in most populations and imaging procedures play a leading role in the diagnosis of these pathologies.
CAUSES OF HYPERBILIRUBINEMIA

PREDOMINANTLY UNCONJUGATED BILIRUBIN

• Excessive biliary pigment formation:
  o Intravascular hemolysis
  o Resorption of hematomas
  o Bone marrow marrow impaired erythropoiesis.
• Decreased liver uptake:
  o Sepsis
  o Prolonged fasting
  o Right cardiac insufficiency
  o Medication (Rifampicin, Probenecid)
• Decreased conjugation:
  o Severe hepatocellular injury (cirrhosis, hepatitis)
  o Sepsis
  o Medication (Cloranfenicol, Pregnadiol)
  o Gilbert syndrome
  o Crigler Najjar syndrome (type I or II)

PREDOMINANTLY CONJUGATED BILIRUBIN

• Decreased liver excretion:
  o Hepatocellular injury (cirrhosis, hepatitis).
  o Cholestasis induced by drugs
  o Sepsis
  o Primary or secondary biliary cirrhosis
  o Dubin-Johnson and Rotor syndromes
• Biliary obstruction:
  o Hepatic
    - Primary sclerosing cholangitis
    - Bacterial cholangitis
    - Fibropolycystic liver disease: Caroli’s disease and bile duct cysts.
    - Primary tumors: hepatocarcinoma, intrahepatic cholangiocarcinoma
    - Metastasis
    - Other intrahepatic lesions: Echinococcosis, abscesses, cysts
    - Portal hypertension of other causes
  o Suprapancreatic
    - Choledocolithiasis
    - Extrahepatic cholangiocarcinoma
    - Gallbladder carcinoma
    - Posttraumatic and postsurgical lesions: stenosis, ischemia, etc
  o Pancreatic
    - Pancreatitis
    - Autoimmune pancreatitis
    - Pancreatic tumors: adenocarcinoma
    - Ampuloma
UNCONJUGATED HYPERBILIRUBINEMIA:

- Excessive biliary pigment formation

  o Intravascular hemolysis and resorption of hematomas: the increased destruction of red blood cells increases the production of unconjugated bilirubin.

  o Bone marrow impaired erythropoiesis: it refers to the premature destruction of red blood cells, before they are released into the blood stream.

- Decreased liver uptake:

  o Sepsis: In this condition, the elevated bilirubin level in plasma consists predominantly of conjugated bilirubin, suggesting that hyperbilirubinemia is mainly caused by impaired canalicular secretion. It may also cause malfunction of the hepatocyte and its inability to conjugate bilirubin.

  o Right cardiac insufficiency: Is the inability of the heart to assure an adequate blood output. The right ventricular insufficiency causes an increase of the pressures in the cavities of the right heart, in the superior vena cava and the suprahepatic veins, with a stagnation of blood in the liver which can lead to edema of the hepatocytes and the subsequent lesser uptake of bilirubin. Imaging findings include suprahepatic ingurgitation and constrast reflux from the right ventricle. Hepatic enhancement may be inhomogeneous caused by hepatocellular edema and blood stasis in the liver. Fig. 1 on page 10

  o Drugs: Some medications like Probenecid, Rifampicin and Cloranfenicol produce a toxic reaction in the liver and the subsequent cell damage that may cause an increased unconjugated bilirubin blood level.

- Decreased conjugation:

  o Severe hepatocellular injury:

    - Cirrhosis: Defined as a consequence of chronic liver disease of many causes (alcoholism, hepatitis B and C, haemochromatosis, etc.) characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules leading to loss of liver function. Due to the severe hepatocellular damage, there is a decrease in bilirubin conjugation and excretion, and therefore jaundice. Imaging features of cirrhosis include
decreased size of the right hepatic lobe and of the medial segment of the left lobe, with compensatory hypertrophy of the caudate lobe and often of the lateral segment of the left lobe. The liver contour frequently has a nodular appearance. Hepatic enhancement is characteristically inhomogeneous and collateral vessels and varices secondary to portal hypertension appear. Fig. 2 on page 10

- **Hepatitis:** Hepatitis can be divided into acute and chronic forms. In acute hepatitis, histologic changes are present primarily in the intralobular portion of the liver with swelling of hepatocytes. Chronic hepatitis is characterized by a portal inflammatory infiltrate with additional fibrous and inflammatory changes surrounding the lobules. These changes lead to an impaired function of the hepatocyte interfering in the bilirubin conjugation process and its excretion.

  - Gilbert syndrome: Autosomal recessive condition characterized by intermittent jaundice in the absence of hemolysis or underlying liver disease. The hyperbilirubinemia is mild and it is due to underactivity of the conjugating enzyme system bilirubin-uridine diphosphate glucuronyl transferase (bilirubin-UGT).

  - Crigler Najjar syndrome: Rare autosomal recessive disorder of bilirubin metabolism, elicited by a lack or deficiency of the enzyme (UGT). Two forms are described: type 1 and type 2. Crigler-Najjar Type 1 is associated with an almost complete absence of the enzyme, which results in very high levels of unconjugated hyperbilirubinemia (up to 50 mg/dL) at birth. Lower levels of serum bilirubin (up to 20 mg/dL) and markedly depressed activity of hepatic UGT are characteristic of type 2 Crigler-Najjar. Treatment with phenobarbital can induce the expression of UGT in patients with type 2 Crigler-Najjar syndrome.

CONJUGATED HYPERBILIRUBINEMIA

- **Decreased liver excretion:**

  - Primary biliary cirrhosis: is a chronic and progressive cholestatic disease of the liver. The etiology is unknown, although it is presumed to be autoimmune in nature. It consists in destruction of the small-to-medium bile ducts, which leads to progressive cholestasis and often end-stage liver disease.

  - Dubin-Johnson syndrome: autosomal recessive disorder caused by a mutation in the gene responsible for the human canalicular multispecific organic anion transporter (cMOAT) protein. This protein mediates (ATP)-dependent transport of certain organic anions across the canalicular membrane of the hepatocyte. Defect in the cMOAT protein results in the impaired hepatobiliary transport of non-bile salt organic anions and is thought to be responsible for the conjugated hyperbilirubinemia and for the accumulation
of hepatocellular pigment seen in the Dubin-Johnson syndrome. Rotor syndrome has a very similar spectrum except for the accumulation of hepatocellular pigment.

- **Biliary obstruction:**
  
  o Hepatic
    
    - *Primary sclerosing cholangitis*: Sclerosing cholangitis is a chronic liver disease caused by inflammation and scarring of the bile ducts of the liver. The underlying cause of the inflammation is believed to be autoimmunity. It is frequently associated with inflammatory bowel, especially with ulcerative colitis. Bile duct cells in patients with sclerosing cholangitis have a strong tendency to undergo malignant degeneration, and cholangiocarcinoma. Imaging findings: the MR cholangiography appearance of sclerosing cholangitis includes dilatation, stenosis, pruning, and beading of the intrahepatic bile ducts. [4] Fig. 3 on page 11
    
    - *Bacterial cholangitis*: Acute cholangitis is a bacterial infection superimposed on an obstruction of the biliary tree most commonly from a gallstone, but it may be associated with neoplasm or stricture. Pathogenesis of acute cholangitis are biliary tract obstruction, elevated intraluminal pressure, and colonization of bile by bacteria from the small bowel.[3]
    
    - *Caroli’s disease*: part of the fibrocystic liver disease is a rare congenital disorder that causes saccular ductal dilatation, with recurrent bacterial cholangitis and stone formation. Imaging findings: images will demonstrate cystic lesions in the liver with the central dot sign that corresponds to the portal vein in the center of the cyst. [7] Fig. 4 on page 12
    
    - *Primary tumors:*
      
      - Hepatocarcinoma: is the most common primary epithelial neoplasm of the liver, usually occurs in association with chronic liver disease. Hepatitis B virus, underlying cirrhosis due to alcohol abuse, hemachromatosis, toxin exposure and aflatoxin exposure are the primary etiologic factors. It may have 3 different growing patterns: Solitary, multifocal, and diffuse growth. The Solitary pattern rarely invades de biliary ducts but it may compress it externally. Jaundice is more plausible when a multifocal or a diffuse growth is seen. Imaging findings: the hypervascular nature of the tumor makes three-phase imaging a critical feature in the detection and characterization of this tumor. It typically presents as an enhancing lesion(s) in the arterial phase with contrast washout in the portal phase. In delayed phases it may present an enhancing fibrotic capsule. Fig. 5 on page 12 The diffusely infiltrative pattern shows an enlarged heterogeneous liver. [5] Fig. 6 on page 13
      
      - Intrahepatic cholangiocarcinoma: is the second most common primary hepatic tumor. Intrahepatic tumors arise from the small ducts and are often diffuse and multicen-tric. There may be solitary tumors or diffuse sclerosing or scirrhous types. Imaging findings:
CT may demonstrate the tumor if the malignancy is nodular and masslike, but tumors of the diffuse sclerosing variety are difficult to detect. The mass is predominantly hypo-attenuating, with irregular margins. Images may demonstrate segmental biliary ductal dilatation because of obstruction. With intravenous contrast material, the mass may demonstrate a variable enhancement pattern. No enhancement, minimal peripheral enhancement, or central enhancement may be depicted. Diffusely infiltrative pattern has a poorly defined appearance with an infiltrative growth pattern. In MRI an intrahepatic mass may be seen as a hypointense lesion relative to normal liver on T1-weighted images. T2-weighted images show predominant isointensity or slight hyperintensity relative to the liver parenchyma in about 64% of cases and marked hyperintensity in 36% of cases. Fig. 7 on page 13

- **Metastasis:** The liver is the most common site of metastases that arise from gastrointestinal malignancies; other primary sites of origin include breast, lung, pancreas, and melanoma. **Imaging findings:** Most liver metastases are multiple, and usually both lobes are involved; in only 10% of cases is metastasis solitary. The appearance of metastatic disease of the liver is variable. Larger tumors may have central low attenuation from necrosis or cystic degeneration, as well as calcifications. Large metastases compress adjacent liver parenchyma, causing atrophy and forming a connective tissue rim. Fig. 8 on page 14

- **Noncirrhotic portal hypertension:** recently described as an antiretroviral toxicity (particularly didanosine exposure) wich is thought to cause focal obliteration of small portal veins. **Imaging findings:** splenomegaly, ascites, collateral veins in the peritoneal cavity, the retroperitoneum, the abdominal wall, and the mediastinum are the most common imaging findings. The portal vein may be enlarged (>13mm). Fig. 9 on page 14

- **Suprapancreatic**
  - **Choledocolithiasis:** Is the most common cause of bile duct obstruction. In 95% of patients the stones have migrated from the gallbladder into the common bile duct. It may have complications such as: cholangitis, acute pancreatitis, fistula, liver abscess, etc. **Imaging findings:** US, TC and MR imaging are helpful in the depiction of bile duct lithiasis. MRI is highly accurate in the diagnosis of bile duct lithiasis. The large majority of stones are seen as T1 and T2 hypointense structures, surrounded by bile. In CT imaging they are seen as hyperattenuating images within the main bile duct. US shows hyperechogenic images with acoustic shadowing.[3] Fig. 10 on page 15

- **Extrahepatic cholangiocarcinoma:** located below the proximal part of the common hepatic duct. Sometimes it could affect the bifurcation being called Klatskin tumor. **Imaging findings:** it is characterized by dilatation
of intrahepatic ducts without extrahepatic ductal dilatation. The mass in or surrounding the ducts is visible on CT/MR in about 40% of cases. The confluence of the right and left ducts may be obliterated with the loss of sharp distinction. The infiltrating tumors, which grow along the duct, and the intraluminal polypoidal tumors are difficult to detect. Exophytic tumors are larger, and the mass is demonstrable as a low-attenuating lesion with lobulation. [1] Fig. 11 on page 16

- **Gallbladder carcinoma:** Cancer of the gallbladder is uncommon (1.2 cases per 100,000 persons in US). The most common risk factor for gall-bladder cancer is gallstones, especially if they are greater than 3cm. Porcelain gallbladders and stippled calcification of the mucosa is thought to carry a higher risk of gallbladder carcinoma. Imaging findings: US, CT an MR may show a mass replacing the gallbladder (40-70%) as well as a heterogeneous focal/diffuse thickening of the gallbladder wall (15-30%) or a polypoid intraluminal mass (15-25%). Fig. 12 on page 16

- **Bile duct cysts:** Part of a congenital fibrocystic disease, a ductal plate malformation of the extrahepatic bile duct, with or without concomitant liver fibrosis. It may also be secondary to a pancreatico-biliary junction anomaly that predisposes to the reflux of pancreatic enzymes into the common bile duct, with the subsequent chemical and inflammatory changes, resulting in weakness and dilatation of the bile duct wall. Imaging findings: at imaging, choledochal cysts appear as cystic or fusiform dilatation of the common bile duct. [7]

- **Posttraumatic and postsurgical lesions:** Stenosis of the bile duct after severe traumatic injury scaring or after heptojejunostomy anastomosis, may cause an upstream dilatation of the biliary tract. After hepatic transplantation, ischemia is an important cause of biliary injury. Bile ducts receive their blood supply from the hepatic artery. Any abnormality leading to decreased arterial flow may cause ischemia. Imaging findings: typical features of fibrotic strictures are short length, limited to the anastomosis, smooth delineation and no mass lesion. It is best evaluated with a MR cholangiography. Bile duct ischemia is seen as multiple irregularities/strictures typically involving both intrahepatic ducts and the proximal common hepatic duct, with bile duct dilatation. Fig. 13 on page 16

**Pancreatic**

- **Pancreatitis:** Acute inflammatory disease of the pancreas producing temporary changes with restoration of normal anatomy and function. Caused by Biliary disease (60%), alcoholism (30%) and other causes as hypertriglyceridemia. Imaging findings: with a two phased CT scan necrosis should be evaluated as non enhancing areas. It can be classified with the Atlanta classification or with the Baltazar classification:
• Grade A, B: edematous pancreatitis with enlargement of the gland.
• Grade C: acute pancreatitis with associated peripancreatic inflammation (inflammation of the surrounding fat tissue and ascites).
• Grade D, E: acute pancreatitis with ill-defined fluid collection/phlegmon. Fig. 14 on page 17

• **Autoimmune pancreatitis**: Is the pancreatic manifestation of IgG4 related sclerosing disease, with numerous extrapancreatic organs affected, such as the bile ducts, gallbladder, kidneys, retroperi-toneum, thyroid, salivary glands, lung, mediastinum, lymph nodes, and prostate, synchronously or metachronously. There are three different patterns: diffuse, focal, and multifocal. Diffuse disease is the most common type, with a diffusely enlarged sausagelike pancreas and a sharp margin and loss of the lobular contour. Focal disease is less common and manifests as a focal mass, often with involvement of the pancreatic head and a milder dilatation of the main pancreatic duct is than in patients with pancreatic adenocarcinoma. Multifocal involvement also may be present. **Imaging findings**: the affected area of the pancreas typically appears hypoechoic at US hypoattenuating at CT, mildly hyperintense at T2-weighted MR imaging, and hypointense at T1-weighted MR. Moderate delayed enhancement with contrast medium is seen in the late phase. The presence of a capsule-like rim or "halo" is common in patients with autoimmune pancreatitis and is believed to represent fluid, phlegmon, or fibrous tissue. [6] Fig. 15 on page 18

• **Pancreas tumors**: Adenocarcinoma is the most common type of pancreatic cancer arising within the exocrine component of the pancreas. 65% presents in the head of the pancreas, thus compressing the common bile duct. **Imaging findings**: high-resolution dual-phase (arterial and portal) contrast material-enhanced CT is the established technique for evaluating pancreatic adenocarcinoma. Most tumors are hypoattenuating, hypointense in T1-weighted images and iso-hyperintense in T2-weighted images. Tumors in the pancreatic head may cause dilatation of both the common bile duct and the main pancreatic duct whereas tumors in the pancreatic body may cause upstream main pancreatic duct dilatation. Atrophy of the pancreas proximal to the tumor is noted in chronic obstruction. Fig. 16 on page 19

• **Ampulloma**: Is a malignant tumor arising within 2 cm of the distal end of the common bile duct, where it passes through the wall of the duodenum and ampullary papilla. **Imaging findings**: typical imaging features include dilatation of the common bile duct and pancreatic duct, abrupt irregular narrowing or occlusion of the distal portions of both ducts ("double duct sign"); enlarged bulging papilla with or without soft tissue mass. Fig. 17 on page 20

• **Pancreatic pseudocyst/cysts**: Pseudoquistic or quistic lesions of other causes (fibropolicystic disease, serous cystadenomas, Von Hippel-Lindau disease),
may be a cause of jaundice, especially if they are present in the head of the pancreas causing a biliary obstruction. **Imaging findings:** these lesions may appear as anechogenic well defined image with US, hypoattenuating masses in CT imaging and hyperintense in T2-weighted MR images.

Images for this section:

![Fig. 1: MR T1-weighted axial view of a patient with right cardiac insufficiency. Note a very heterogeneous signal intensity, specially seen in the right hepatic lobe.](image-url)
Fig. 2: Liver cirrhosis. CT scan show a recanalized umbilical vein (arrow) and splenomegaly, suggesting secondary portal hypertension.
**Fig. 3:** MR cholangiopancreatography shows multiple strictures (arrows) in intrahepatic bile ducts. Signal voids on the left represent high-grade strictures. On the right, dilatations are also seen in left lobe intrahepatic bile ducts.

**Fig. 4:** A. CT scan, axial view showing severe saccular dilatations of the intrahepatic bile ducts. B. MR T2-weighted coronal image. Central "dot sign" arrows in A and B.
**Fig. 5:** A. CT scan arterial phase shows an hyperenhancing lesion in segment VIII with a central necrotic area. B. CT scab portal phase shows contrast washout and an capsule enhancement (arrows).

**Fig. 6:** A. Ultrasonography shows a markedly heterogeneous liver. B. CT scan shows a severely enlarged liver, with heterogeneous attenuation. Histological study confirmed a diffuse infiltrative hepatocarcinoma.
**Fig. 7:** A. MR T2-weighted images show intrahepatic duct dilatation. B. A lower image shows an intrahepatic mass (arrow) slightly hyperintense relative to the liver parenchyma.

**Fig. 8:** Contrast-enhanced CT scan taken in the portal venous phase shows multiple hypervascular metastatic deposits from a carcinoid tumor.
Fig. 9: CT scan portal venous phase shows collateral veins with dilated tortuous splenic vein/varices at the splenic hilum. Recanalization of umbilical vein and an enlarged portal vein (arrows) are consistent with portal hypertension in an HIV patient with no liver disease shown.
**Fig. 10:** A. CT MPR coronal view in a patient with jaundice and abdominal pain, shows at least one hyperattenuating stone within the common bilu duct. B. MR cholangiopancreatography in the same patient shows there are actually three lithiasis.

**Fig. 11:** A. MR T2-weighted imaging shows dilated left and right intrahepatic ducts. B. A 3D reconstruction shows absence of the confluence of the right and left hepatic bile ducts and a normal common bile duct, consistent with a Klatskin tumor.

**Fig. 12:** Gallbladder carcinoma in two different patients. A. Diffuse thickening of the gallbladder wall with marked enhancement. Dilated intrahepatic bile duct is also seen. B. CT axial image shows a mass replacing the gallbladder.
Fig. 13: CT scan with MIP reconstruction shows a hepatic artery stenosis (thick arrow) in a patient with liver transplantation. Secondary biliary duct ischemia with subsequent dilatation is also seen (thin arrow).
Fig. 14: CT scan, portal venous phase image shows an enlarged pancreatic head (arrow), with inflammatory changes in the surrounding fat tissue and ascites. consistent with acute pancreatitis, Baltazar grade C.
Fig. 15: A-B. CT scan shows diffuse enlargement of the pancreatic gland with the "halo" sign around the body (arrow in A). C. PET scan shows diffuse 18-FDG uptake.
**Fig. 16:** Pancreatic head adenocarcinoma (arrow) with secondary bile duct obstruction. A drainage is seen in the common bile duct.

**Fig. 17:** Ampulloma in two different patients. A. CT scan showing dilatation of the main pancreatic duct and the common bile duct: "double duct sign" (arrow). B. CT scan, axial view shows a hyperattenuating lesion in the duodenum wall. Hystologically, an ampulloma was demonstrated.
Conclusion

Jaundice is a clinical sign that can be due to several pathologies. Radiologists must be familiar with bilirubin metabolism and causes of jaundice to specify the most suitable diagnostic procedure. In this exhibit we have presented cases of unconjugated and conjugated hyperbilirubinemia that have a radiological imaging depiction. When conjugated hyperbilirubinemia is present imaging techniques are crucial to identify the cause.

Personal Information

References