Symptoms and Syndromes

13 Cholestasis

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13 Cholestasis

1 Definition

Cholestasis is defined as a disorder of cholepoiesis and bile secretion as well as a mechanical or functional stoppage of the bile flow in intrahepatic or extrahepatic bile ducts – with bile components passing into the blood. • *Cholestasis can occur both with and without jaundice.*

Morphology: The morphologist uses the term cholestasis to describe the presence of bile in the hepatocytes as well as in hypertrophic Kupffer cells (= *cellular bilirubinostasis*), particularly in the form of inspissated bile droplets and copper within the more or less dilated canaliculi (= *canalicular bilirubinostasis*). • In extrahepatic cholestasis, bile is additionally found within the likewise mostly dilated interlobular bile ducts (= *ductular bilirubinostasis*) as well as in the parenchyma in the form of *"bile infarcts"* or *"bile lakes"*.

Pathophysiology: The biochemist defines cholestasis as a decrease in the secretion of bile as well as a reduction in the proportion of water, together with a respective effect on the substances dissolved in it.

Clinical aspects: The clinician diagnoses cholestasis by the increase in bile acids, special enzymatic markers and cholesterol in the serum.

► The *principal biochemical symptom of cholestasis* is the rise in bile acids in serum (as well as changes in its spectrum) in combination with an increase in enzymatic markers of cholestasis (AP, LAP, γ-GT, 5′-nucleotidase). Cholestasis is directly related to the metabolism of bile acids. • In clinical terms, the subsequent rise in activity of enzymatic markers of cholestasis may be attributed to cholestasis, yet these enzymes are not necessarily specific to this condition. (s. p. 89)

► Dysfunction in the metabolism of bile acids (= *cholestasis*) is often combined with an additional dysfunction in bilirubin metabolism (= *jaundice*). The rise in bilirubin is the main biochemical and clinical symptom of jaundice; it is based on a disorder of bilirubin metabolism. Thus cholestasis is related not directly but indirectly to jaundice. • Depending on the constellation of the biochemical and clinical findings, the term *"jaundice with cholestasis"* or *"cholestasis with jaundice"* can be applied. (s. tabs. 12.1, 12.2, 12.4; 13.1) • *The main clinical sign of advanced cholestasis is pruritus.*

Various hepatobiliary diseases remain unchanged as either **cholestasis** or **jaundice.** • Often, however, a *combination of both disorders* is present from the very beginning or appears during the course of disease.

2 Pathogenesis

The liver cell is a polar unit. • The resorptive processes take place at the sinusoidal and lateral membrane, the secretory processes on the surface of the canaliculi. The cytoskeleton (microfilaments, microtubules, intracellular membranes) maintains the polar orientation of the hepatocyte. (24, 33, 42, 44, 71, 80) (s. fig. 13.1)

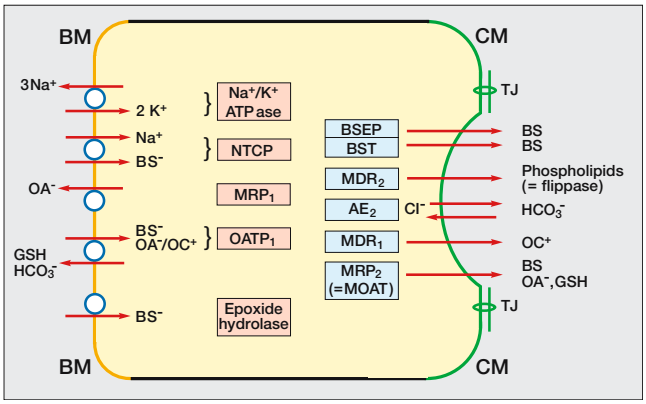

Fig. 13.1: The hepatocyte as a polar unit. • *Major hepatocellular transport systems:* CM = canalicular membrane, BM = basolateral membrane, TJ = tight junctions, BS^- = bile salts, OA^- = organic anions, OC^+ = organic cations, GSH = reduced glutathione, AE_2 = ATP-dependent anion exchange (Cl/HCO_3^-; GSH), BST = ATP-dependent bile acid transporter, NTCP = sinusoidal Na^+-dependent taurocholate cotransporting protein, $OATP_1$ = sinusoidal Na^+-independent organic anion (and cation) transporter protein, BSEP = bile salt export pump for monovalent bile salts, MRP_2 = canalicular multispecific organic anion transporter (= MOAT), MDR_1 = ATP-dependent organic cation transporter, MDR_2 = ATP-dependent phospholipid transporter (= flippase), MRP_1 = sinusoidal multidrug resistance-associated protein

2.1 Obstructive cholestasis

Obstructive cholestasis – initially often without jaundice, thereafter generally with jaundice – is caused by a mechanical impediment of the bile flow. Because of this, the bile flow is reduced and biliary stasis is generated, which, depending on the localization of the impediment, subsequently affects the bile ducts of (*1.*) the entire liver or (*2.*) only certain subzones of the liver.

Even in cases of a total obstruction with jaundice, there is no total stoppage of bile secretion due to the residual function of the hepatocytes. What happens, in fact, is that a certain form of **circulation of intrahepatic bile acids** is maintained by way of resorption processes taking place in the bile capillaries and mechanisms of regurgitation occurring at the tight junctions. This circulation of bile acids mainly runs via the periportal sections of the hepatic lobules, so that biliary thrombi are only rarely detectable here – even in cases of prolonged cholestasis. • In obstructive cholestasis, with its secondary repercussions on bile capillaries and hepatic cells, including *morphological changes,* it is probable that *functional disorders* in the polarity of the hepatocytes will ultimately appear.