Vascular disorders of the liver

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Vascular disorders of the liver can be produced by a variety of lesions affecting various parts of the hepatic vasculature : the capillaries - the so-called sinusoids ; the hepatic arterial tree from the large arteries to the arterioles ; the portal venous system from the portal veins to the portal venules ; and the hepatic venous system from the central venules to the major hepatic veins. Obviously, for clinical consequences to arise, injury to the microcirculation must be diffuse, whereas limited injury to the large blood vessels can have serious consequences. In this talk, I shall consider only disorders of the portal veins and disorders of the hepatic veins and I will focus mainly on thrombosis.

Portal vein thrombosis

The causes of portal vein thrombosis are usually unknown and not apparent at presentation (1,2). Therefore, a systematic investigation has to be carried out. The two most common causes are primary myeloproliferative disorders and protein S deficiency, each accounting for 25% of the cases. All the known hereditary thrombophilias, acquired thrombophilic states and risk factors for thrombosis, have been reported in association with portal vein thrombosis. Morevover, combination of these causal factors is encountered in about 15% of the patients. A focal triggering factor within the abdomen is surprisingly uncommon, being found in less than 25% of the cases. Overall, 20% of the cases of portal vein thrombosis still remain unexplained at present. The local factors most commonly incriminated include injury to the portal venous system (cannulation, section, ligation, anastomosis, splenectomy) ; portal venous stasis (due to cirrhosis, obliterative portal venopathy, or hepatic venous outflow block) ; amoebic or pyogenic abscesses ; and inflammatory conditions within the portal venous territory (appendicitis, diverticulitis, inflammatory bowel disease, pancreatitis, and cholangitis).

Cirrhosis deserves a special mention. In 80% of patients with cirrhosis and portal venous obstruction, there is invasion of the portal veins by hepatocellular carcinoma (3). Conversely, in 20% of patients with hepatocellular carcinoma and portal venous obstruction there is a thrombus without tumorous invasion (3). In patients with cirrhosis without hepatocellular carcinoma, the prevalence of portal vein thrombosis is related to the severity of liver disease, being less than 1% in Child-Pugh class A patients (4), and up to 15% in patients candidates for liver transplantation or portosystemic shunting (Francoz C, *et al.* unpublished results). However, portal vein thrombosis is very common in explanted cirrhotic livers (5). Small mural thrombi are found in about 60% of the intrahepatic portal veins. Intimal fibrosis (a sequella of previous thrombosis) affects 25% of the large veins, and 38% of the small veins. In the past, surgery for portal hypertension has been a major cause of portal vein thrombosis in the past. At present, development of portal vein thrombosis in a patient with cirrhosis in a good condition suggests the presence of an underlying thrombophilia : in a recent study, at least one among three thrombophilic mutations (factor V Leiden mutation, prothrombin gene mutation and homozygous C677T MTHFR polymorphism) was found in 70% of cirrhotic patients with, but only 14% of cirrhotic patients without portal vein thrombosis (6).

Upstream from the thrombus, there is little consequences for the gut as long as the patent mesenteric venous arches can act as a collateral circulation. However, when these arches are involved by thrombosis, small bowel ischemia occurs and necrosis may happen (7). Downstream to the thrombus, the livers appears relatively well preserved from ischemia thanks to several mechanisms including the so-called buffer response of the hepatic artery, and rapid development of a collateral hepatopetal porto-hepatic circulation. The development of these collateral veins in the porta hepatis gives rise to the so-called portal cavernoma. The cavernoma, however, is inefficient in relieving the block on the portal vein and portal hypertension ensues. Recurrent gastrointestinal bleeding is the major complication affecting patients with long standing portal vein thrombosis (8). The second major complication in these patients is recurrent thrombosis, usually in the portal venous territory, but also in other venous beds (8). Currently, stenosis of the bile ducts due to compression by the portal collaterals is emerging as a most important source of morbidity, in the form of cholangitis, cholecystitis, biliary stones and chronic cholestasis (9,10).

Recently a great interest has been paid to the consequences of the obstruction of one major branch of the portal vein, the other branch remaining patent. The

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hepatic parenchyma in the obstructed territory undergoes atrophy due to apoptosis ; there is sinusoidal dilatation ; necrosis may also occur when the obstruction is sudden and complete (11,12). However, in the unobstructed territory, the hepatic parenchyma undergoes hypertrophy related to hepatocellular proliferation. The mechanisms signaling this adaptation are not yet understood (12,13).

Recently also, the entity called obstructive portal venopathy has been better characterized (14). This entity corresponds to the so-called non cirrhotic intrahepatic portal hypertension and it overlaps with nodular regenerative hyperplasia and septal cirrhosis. It is characterized by the obstruction of intrahepatic portal veins albeit with patent extrahepatic veins. The most common cause for this entity is schistosomiasis. In western countries, it is associated with an underlying thrombophilia or a thrombophilic condition in half the cases (14). The most characteristic feature of this condition is the development of a microscopic cavernoma within the portal spaces. In addition there is fibrous enlargement of the protal tracts and sinusoidal fibrosis.

The diagnosis of portal vein thrombosis has become easy with the wide spread availability of CT scan and Doppler ultrasound. The main diagnostic challenge is to identify a possible cause of portal vein thrombosis using imaging for local factors, and hematological investigation for the thrombophilic states and hereditary thrombophilias.

Treatment of portal vein thrombosis is discussed differently at the stage of recent thrombosis and at the stage of cavernoma. At the stage of recent thrombosis, repermeation of the portal vein can be expected in over 75% of the cases promptly treated with anticoagulation alone (15). It is recommended to maintain anticoagulation for at least 6 month. In patients with portal cavernoma, beta-adrenergic blocking agents and endoscopic therapy appear as efficient for primary or secondary prophylaxis of gastrointestinal bleeding as they are in patients with cirrhosis (8). It has been shown that anticoagulation can be given to patients with portal cavernoma, without increasing the risk or the severity of gastrointestinal bleeding (8). Because it has also been shown to significantly decrease the risk of recurrent thrombosis (8), anticoagulation can also be proposed to patients with portal cavernoma, especially when there is an underlying thrombophilic condition and when no treatable local factor has been documented.

Hepatic vein thrombosis

Budd-Chiari syndrome is characterized by the obstruction of the hepatic venous outflow tract, be the obstruction at the level of small hepatic veins, large hepatic veins, or suprahepatic segment of inferior vena cava (16). Hepatic vein thrombosis (with or without inferior vena cava involvement) is the main mechanism causing Budd-Chiari syndrome. The so-called veno-occlusive disease (now best denominated sinusoidal obstruction syndrome) is characterized by non thrombotic occlusion due to toxic injury to the sinusoids (17). It is considered a separate entity. Thrombosis limited to hepatic venules is very rare. Hepatic vein or inferior vena cava involvement by thrombosis can take 3 different aspects depending on the stage at which it is discovered : a fresh thrombus, a localized fibrous stenosis, or complete obliteration of the vein (18).

The recognized causal factors for hepatic vein thrombosis are qualitatively similar to those for portal vein thrombosis, although occurring at a different frequency (1). Primary myeloproliferative disorder, protein C deficiency, factor V Leiden and antiphospholipid syndrome are the leading causal factors. Combination of causal factors is fifty-fold as frequent as expected. Local factors are rarely identified. Oral contraceptive use or pregnancy may play a role in conjunction with an underlying causal factor.

Obstruction of the hepatic veins leads to two different types of consequences. First, raised sinusoidal pressure explains congestion, portal hypertension, increased lymph production resulting in the formation of protein-rich ascitic fluid, and development of collaterals that bypass the obstructed portion of the hepatic veins and tend to restore hepatic perfusion. Second, sudden interruption in hepatic venous blood outflow explains ischemic necrosis and the resulting liver insufficiency. There are adaptative mechanisms able to restore hepatic perfusion, including increased arterial blood flow, increased portal pressure, and development of intrahepatic and extrahepatic venous collaterals.

Recently, emphasis has been placed on the frequent association of hepatic vein thrombosis with portal vein thrombosis, at least in the most severe cases since these data were derived from necropsy studies or examination of explanted livers (19,20). Intrahepatic portal venous thromboses are found in more than half of these cases, with an irregular distribution. The areas where both portal veins and hepatic veins are obstructed undergo atrophy (infarcts or parenchymal extinction). The areas with obstructed portal veins but patent hepatic veins undergo hypertrophy in an exuberant form, resulting in the development of regenerative macronodules. At imaging, these macronodules closely resemble hepatocellular carcinoma (19,21).

Hepatic vein thrombosis can run a long asymptomatic course and there is little clinicopathological correlation, acute presentation being commonly associated with acute histopathological features superimposed on chronic ones (22). There are 3 main variants of clinical manifestations. The acute variant includes upper abdominal pain, liver enlargement, ascites of recent onset, increased serum transaminases, decreased coagulation factors, and impaired renal function (23). The chronic variant, which is the most common, presents as a decompensated liver disease. In the asymptomatic variant, hepatic vein thrombosis is discovered incidentally.

The increased recognition of the asymptomatic cases is likely related to the progresses in imaging procedures as well as better awareness of the entity. The evolution can be complete spontaneous remission with or without recurrent manifestations or an unremitting downward course. Half the patients have an excellent 10-yr survival rate (> 90%), while the other half have a 50% 10-yr mortality rate with most fatalities occurring in the first 12 or 18 months following presentation (24,25). Prognosis of hepatic vein thrombosis syndrome is mainly related to associated portal vein thrombosis. Other factors with independent prognostic value are age, and Child Pugh score. Taking into account the clinicopathological form improves prognostication for survival (Langlet P. *et al.* J Hepatol 2003, in press) (26).

Diagnosis can be made using non-invasive procedures in most cases (27). The most specific and sensitive signs are the demonstration of an altered blood flow within the hepatic veins or a hepatic venous collateral circulation. Doppler ultrasound is an accurate method for making diagnosis. Its limitations lie in the experience of the operator and the body habitus of the patient. Magnetic resonance imaging is less effective in demonstrating abnormal flow but is not operator dependant. Hepatic venography, which is no more required for diagnosis, still remains an irreplaceable tool for delineating the venous lesion and planning intervention therapy.

Owing to the rarity of the disease, therapy for hepatic vein thrombosis has not been scientifically evaluated. Anticoagulant therapy is logical and appears to have improved the outcome of the disease in the last 2 decades (28). Symptomatic therapy for bleeding from portal hypertension and ascites should always be undertaken. In patients with symptomatic disease, repermeation of the obstructed hepatic outflow tract can be attempted using non-surgical procedures such as percutaneous angioplasty with stenting when there are short-length stenoses on the hepatic veins or inferior vena cava (29). Repermeation of recent thrombosis with thrombolytic agents is not yet proved as effective and safe. Surgical portacaval shunts do not appear to impact much on survival, probably because of high operative mortality and high incidence of late shunt stenosis (26,30,31). However, patients surviving the operation and with a shunt remaining patent have an excellent long term outcome. TIPS appears promising because of an extremely low procedure-related mortality (32). However, on the long-term the obstruction rate is expected to be high and follow-up studies are awaited. Based on uncontrolled data, liver transplantation in the most severe cases can be expected to increase 10-yr survival rate from 50% to 70% (33).

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