ETIOLOGY OF PORTAL HYPERTENSION

Part of "11 - PORTAL HYPERTENSION"

Portal hypertension can be caused by any disease interfering with blood flow at any level within the portal venous system. According to anatomic location, the diseases causing portal hypertension are classified as prehepatic (diseases involving the splenic, mesenteric, or portal veins), intrahepatic (acute and chronic liver diseases), or posthepatic (diseases interfering with the venous outflow of the liver) (5) (Table 11.1). Cirrhosis of the liver is by far the most

common cause of portal hypertension in the world, followed by hepatic schistosomiasis. All other causes account for fewer than 10% of cases, which is why these cases are sometimes referred as *noncirrhotic portal hypertension.*

TABLE 11.1. ETIOLOGY OF PORTAL HYPERTENSION

Prehepatic Portal Hypertensive Syndromes

Prehepatic portal hypertension is an infrequent condition in which increased portal pressure is caused by obstruction of the portal venous tree before it enters the liver. The site of obstruction may be limited to the splenic or mesenteric veins, but most commonly the portal vein is involved. Obstruction may be caused by congenital abnormalities or, more usually, by various underlying diseases that affect part or all of the vessels of the portal venous system. In all these conditions, it is essential to obtain accurate anatomic information about the site and extent of the obstruction because it may affect therapeutic decisions.

Portal Vein Thrombosis

Portal vein thrombosis is the most frequent cause of prehepatic portal hypertension. In children, a history consistent with omphalitis or umbilical catheterization can be often obtained. In adults, the cause of portal thrombosis is less frequently identified. In adults, portal vein thrombosis may be caused by intraabdominal infections, the use of oral contraceptives, abdominal trauma, pregnancy, autoimmune diseases, or underlying disorders favoring a hypercoagulative state (e.g., myeloproliferative disorders or inherited or acquired coagulation factor disorders) (6). Portal vein thrombosis may be a complication of cirrhosis (7). However, the prevalence of portal thrombosis in cirrhotic patients is low (probably <1%), whereas it is a frequent event after splenectomy and in patients with hepatocellular carcinoma (~25%). Several authors have pointed out that endoscopic injection sclerotherapy may promote portal vein thrombosis. Splenectomy is also recognized as an important factor favoring portal thrombosis. Even when a possible cause for the thrombosis is identified, such as an intraabdominal infection, investigations have shown that in many cases this has served to trigger thrombosis in a patient with an

underlying prothrombotic condition (6,8). In our experience, myeloproliferative disorders and congenital coagulation abnormalities are the more frequently encountered conditions. It is therefore mandatory to rule out a prothrombotic disease in any case of portal vein thrombosis. In the majority of adult cases, chronic portal vein thrombosis is diagnosed after an episode of bleeding from ruptured esophageal varices or during a routine evaluation, whereas in children it is more frequently diagnosed after splenomegaly has been detected.

Variceal bleeding is much better tolerated in patients with prehepatic portal hypertension than in cirrhotic patients because the former do not have liver failure. Ascites and encephalopathy may develop following bleeding, although very infrequently. In these cases, a diagnosis of concomitant liver disease should be considered.

In some rare cases, the diagnosis is made in the acute phase of the disease, and the manifestations of acute portal vein obstruction are mixed with those of the initiating factor, such as recent surgery or abdominal infection. Patients have abdominal pain and fever. Diarrhea, ileus, and gastrointestinal bleeding resulting from intestinal infarction

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may be present. The severity of these symptoms is variable. The clinical suspicion of portal thrombosis should prompt ultrasonographic examination of the portal system. The identification of solid echoes within the portal vein and the absence of flow signals when pulsed Doppler equipment is used confirm the diagnosis. Echo enhancement may be useful. Magnetic resonance imaging (MRI) and helical computed tomographic (CT) scans are very useful, although not mandatory if ultrasonography clearly shows portal vein thrombosis. When these noninvasive techniques do not demonstrate the site and extent of portal vein thrombosis, other diagnostic procedures, such as angiography, should be used. Angiography is also used in selected cases, especially when a surgical approach is being considered. Retrograde wedged hepatic venography with the use of carbon dioxide as a contrast agent may also be useful.

In the chronic phase, portal venous thrombosis is associated with the development of new vascular channels that bypass the obstruction, so that the portal vein takes on the appearance of a cavernoma. This is best shown at angiography, but also at abdominal ultrasonography. Patients with portal vein obstruction exhibit the same hemodynamic abnormalities as those with any other type of portal hypertension. Thus, the systemic circulation is characterized by a hyperdynamic state, with increased blood volume and cardiac output and reduced arterial pressure and peripheral vascular resistance (9). The splanchnic circulation is also hyperdynamic, with increased inflow of blood into the portal venous system. Serum biochemistry shows either no abnormalities or a mild elevation of globulins, and the hematologic examination may disclose a variable degree of hypersplenism, evidenced by leukopenia, thrombocytopenia, and anemia. The treatment of patients with portal vein thrombosis is usually a challenge, especially those in whom the thrombus extends to the mesenteric and splenic veins. The underlying condition potentially responsible for the vascular occlusion should be treated, if possible, and anticoagulation is recommended because it is associated with lower rates of rebleeding. The role of prophylactic pharmacologic therapy with propranolol or nadolol has not yet been adequately explored. However, a good clinical response to propranolol is usually noted, the incidence of bleeding with propranolol prophylaxis being quite low. The treatment of acute

episodes of gastrointestinal hemorrhage is similar to that for episodes of variceal bleeding in patients with cirrhosis. After hemostasis has been achieved, patients should receive elective treatment to prevent rebleeding. Most patients undergo endoscopic therapy (injection sclerotherapy or band ligation of the varices), which may reduce the proportion of patients requiring surgery. Surgery is strongly discouraged in children and should never be attempted in patients who have not bled. Distal splenorenal shunt is the most useful operation, but this is possible only when the splenic vein is patent. Mesocaval graft shunts are sometimes possible. Other procedures, such as esophageal transection or splenectomy and ligation of the varices, are less useful because of the high frequency of gastric varices and the high index of late rebleeding secondary to recurrent varices.

In cases of recent thrombosis, direct thrombolytic therapy through a catheter introduced into the portal vein (either percutaneously or by a transjugular approach) may be useful. However, recanalization has also been observed with the use of oral anticoagulation, provided it is initiated early after diagnosis (10). This is the usual recommended treatment in clinical practice. Spontaneous recanalization is possible.

TIPS reestablishes the patency of the portal vein by stenting the thrombosed areas. This is sometimes possible in instances of chronic portal vein thrombosis.

Splenic Vein Thrombosis

The main causes of isolated splenic vein thrombosis are chronic pancreatitis and carcinoma of the pancreas (11). Occasionally, splenic vein thrombosis has been described in association with retroperitoneal infection or retroperitoneal fibrosis.

Usually, splenic vein obstruction is diagnosed after an episode of bleeding related to gastric varices. Physical examination reveals an enlarged spleen; the results of biochemical determinations are usually normal, whereas hematologic parameters may indicate hypersplenism. Gastric varices are a prominent (if not the only) endoscopic finding in these patients. The diagnosis is established by ultrasonography and splenic artery angiography. It should be noted that nonvisualization of the splenic vein at splanchnic angiography is not unequivocal evidence of splenic vein thrombosis. False-positive results are frequent in patients with marked splenomegaly. In these cases, MRI can be very helpful.

Unlike subjects with portal thrombosis, patients with isolated splenic vein obstruction should be treated surgically because splenectomy is a curative operation and not associated with high rates of morbidity and mortality. However, patients without previous bleeding must be informed in detail of the risks and long-term care that they will require after splenectomy before they opt for surgery.

Congenital Stenosis of the Portal Vein

It is important to consider this condition in children with prehepatic portal hypertension. The stenosis may be found at any point along the portal vein, but the hepatic hilus and the middle of the trajectory of the vein are particularly common locations. As in other patients with prehepatic portal hypertension, the disease is usually diagnosed after an episode of gastrointestinal bleeding from ruptured gastroesophageal varices. The physical

examination may show

splenomegaly and subcutaneous collateral vessels. Parameters of liver function remain within the normal range, and ultrasonography shows patency of the portal vein, thus suggesting a false diagnosis of intrahepatic portal hypertension. However, liver histology is normal, as are hepatic venous pressures. Careful ultrasonographic examination of the portal vein and analysis of the venous phase of splanchnic angiography may reveal the stenosis, which can then be confirmed by measuring the venous pressure along the portal vein and demonstrating a pressure gradient at the location of the stenosis. These children can be managed medically, by transluminal balloon angioplasty (with or without stenting), or surgically.

Extrinsic Compression of the Portal Vein

Portal hypertension resulting from compression of the portal vein by a mass or a process located in the vicinity of its trajectory is an unusual condition. However, the splenic vein may be compressed by benign or malignant disease of the pancreas or by retroperitoneal fibrosis.

Partial nodular transformation of the liver is an infrequent disease of unknown origin characterized by the appearance of large nodules (up to 8 cm) in the hilar area of the liver. Serum liver chemistries are usually normal, and the condition is diagnosed either after an episode of bleeding from esophageal varices or during the diagnostic workup of an enlarged spleen. Pathologic examination shows the hilar nodules, which are composed of normal hepatocytes with minimal fibrosis, and a normal appearance of the surrounding liver. The nodules compress the portal vein, which on portography shows a characteristic smooth narrowing at the hepatic hilum.

Arteriovenous Fistulae in the Portal Venous System

Arteriovenous fistulae in the spleen and splanchnic vascular bed may present with portal hypertension, ascites, and varices. About one third of patients have abdominal pain, and in some of these cases, it is possible to hear an abdominal bruit. The location of arteriovenous fistulae may be intrahepatic or extrahepatic (e.g., in the spleen or portal vein). They may be of congenital origin, associated with the Rendu-Osler-Weber syndrome, or caused by trauma. Intrahepatic arterioportal fistulae may be caused by liver biopsy or other invasive procedures. In other cases, fistulae are observed within a hepatocellular carcinoma. In patients with cirrhosis, the development of an intrahepatic arteriovenous fistula may markedly aggravate portal hypertension. In rare cases, an aneurysm of the hepatic artery may rupture into the portal vein and give rise to a fistula and portal hypertension. Aorta-portal fistulae or intrasplenic arteriovenous fistulae are infrequent complications of abdominal wounds.

Treatment of these patients by percutaneous arterial embolization is usually feasible. Otherwise, surgical ligation of the fistula may be required. These procedures are followed by total or partial normalization of the portal pressure. Arteriovenous fistulae increase the portal blood flow, and this may be the unique situation in which the portal pressure increases without an increased resistance to portal blood flow. However, evidence

suggests that secondary “hepatoportal sclerosis,” with fibrosis of portal radicles and thickening and sclerosis of the portal veins, may develop in response to an “arterialized” portal system. This is probably the reason why in some of these patients, portal hypertension is not entirely corrected despite surgical closure of the fistula (12).

Splenomegaly

Splenomegaly in the setting of hematologic or deposit diseases, such as leukemia, lymphoma, polycythemia vera, and myelophthisis with myeloid metaplasia, is thought to produce complications of portal hypertension, including ascites and variceal hemorrhage, as a consequence of an increase in portal blood flow. However, in most cases, the primary disease also infiltrates the liver, and portal hypertension is mostly caused by an increased resistance to portal blood flow. This is why splenectomy frequently does not normalize the portal pressure.

Intrahepatic Causes of Portal Hypertension

Intrahepatic causes of portal hypertension have been classified according to the anatomic zone of obstruction to portal blood flow within the liver and according to the results of hepatic vein catheterization (see below). Hence, these syndromes are divided into presinusoidal (with normal “wedged” pressure), sinusoidal (with increased wedged pressure and normal “free” pressure), and postsinusoidal categories (with increases in both wedged and free hepatic venous pressures). Some diseases cause lesions at several sites.

These liver diseases (Table 11.1) are fully discussed in other chapters. The specific aspects related to portal hypertension are briefly reviewed here.

Schistosomiasis

Portal hypertension is the consequence of a granulomatous reaction to the deposition of parasite eggs in the portal venules. The inflammatory response leads to fibrosis and obliteration of the portal venules, with manifestations of portal hypertension in the absence of significant hepatocellular injury. As the disease progresses, fibrosis extends into the sinusoids, and the hemodynamic pattern and clinical course then resemble those of liver cirrhosis.

Sarcoidosis

Portal hypertension is an infrequent manifestation of hepatic sarcoidosis. Sarcoid granulomas frequently localize in the portal areas of liver lobules and injure portal venules. Early disease is predominantly presinusoidal, with normal sinusoidal pressure, whereas advanced disease leads to fibrosis and cirrhosis.

Myeloproliferative Diseases

Myeloproliferative diseases may cause intrahepatic portal hypertension as malignant cells directly infiltrate the liver.

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia is a nonspecific reaction to a variety of injuries (see Chapter 40). It is characterized by a nodular transformation of the hepatic parenchyma without fibrous tissue between the nodules. The cause of nodular regenerative hyperplasia seems to be heterogeneity of the blood supply. Whereas acini with normal or increased blood flow hypertrophy, others, with decreased blood flow, atrophy. This process may be the result of diseases that decrease the blood flow in the portal venules, in most cases as a result of portal thrombosis, and is probably the main mechanism leading to portal hypertension in this condition. Compression of the portal venous tract by the nodules may also play a role.

Primary Biliary Cirrhosis

The development of portal hypertension in the initial stages of primary biliary cirrhosis (before the development of cirrhosis) is thought to be caused by injury of portal venules at the portal tracts, which promotes a presinusoidal type of portal hypertension. Progression of the disease, with the development of fibrous tracts, adds a sinusoidal component. This is always present when the disease reaches stage IV.

Idiopathic Portal Hypertension

Idiopathic portal hypertension is known by different names, including *Banti syndrome, noncirrhotic portal fibrosis,* and *hepatoportal sclerosis.* The syndrome is recognized predominantly in Japan and India. In India, up to 30% of portal hypertensive patients have this disease, with a male predominance noted.

Variceal bleeding is the main clinical manifestation of idiopathic portal hypertension; ascites, encephalopathy, and other signs of liver failure are encountered only in late stages of the disease. Variceal hemorrhage is usually well tolerated, and endoscopic techniques or portacaval anastomosis are associated with low rates of rebleeding and death.

The etiology of idiopathic portal hypertension has not been explained satisfactorily. Exposure to toxins (arsenic and others) or infectious agents has been postulated, without confirmation. It has been suggested that idiopathic portal hypertension and idiopathic portal thrombosis may be part of the same spectrum, in which the lesion of the portal branches would affect the distal intrahepatic part of the portal tree in idiopathic portal hypertension and the more proximal branches in portal thrombosis.

In idiopathic portal hypertension, the liver surface may be pseudonodular. This fact should be taken into account so that the disease is not confused with liver cirrhosis. Patients with idiopathic portal hypertension must be distinguished by liver biopsy from patients with well-compensated cirrhosis.

Toxicity Caused by Vinyl Chloride, Arsenic, Vitamin A, Mercaptopurine, Azathioprine, Thioguanine, and Other Agents

A variety of drugs and chemicals have been associated with the development of portal hypertensive liver disease in the absence of cirrhosis. Among these, arsenic is a well-

known cause of portal hypertension. Probably a consequence of vascular injury, a wide spectrum of arsenic-related lesions are recognized: angiosarcoma, perisinusoidal fibrosis, peliosis hepatis in association with angiosarcoma, and venoocclusive disease with centrilobular sinusoidal dilatation and perisinusoidal fibrosis. Other etiologic agents in addition to arsenic include vinyl chloride, vitamin A, busulfan, chlorambucil, mercaptopurine, and azathioprine. They all cause lesions with many similarities to those of idiopathic portal hypertension.

Acute and Fulminant Viral Hepatitis

Portal hypertension with all its complications has been described in severe acute hepatitis and fulminant hepatic failure of various causes. A significant correlation has been demonstrated between the severity of portal hypertension (assessed by hepatic vein catheterization) and the severity of hepatitis (indicated by encephalopathy, elevation of serum bilirubin and albumin levels, and coagulopathy). Histologically, portal hypertension seems to correlate with the degree of collapse of the sinusoids and reduction in the intrahepatic vascular space resulting from hepatic necrosis.

Acute Fatty Liver of Pregnancy

A moderate degree of portal hypertension is frequently found in patients with acute fatty liver of pregnancy. It is thought to be caused by compression of the sinusoids by the microvesicular steatosis.

Posthepatic Portal Hypertension Syndromes

Posthepatic obstruction can take place in the IVC or at the level of superior vena cava or right atrium. It may occur in any disease in which right-sided heart pressures are increased.

Acute Fatty Liver of Pregnancy

The causes of mechanical obstruction of the inferior vena cava (IVC) include venous thrombosis, tumor, cysts, and abscesses. Membranous obstruction may be caused by a fibrous web located above the hepatic veins. The clinical presentations of these extrahepatic syndromes overlap with those of intrahepatic postsinusoidal syndromes, such as Budd-Chiari syndrome or venoocclusive disease with congestive hepatomegaly, which may be painful and associated with ascites and variceal bleeding. The presence of venous collaterals on the abdominal wall and edema in the lower extremities may suggest the presence of IVC obstruction.

Membranous obstruction of the IVC is most commonly encountered in young adults in the Far East and Africa. Its course is subacute, in contrast to the usually acute presentation of thrombotic occlusion of the IVC.

Angiography demonstrates a filling defect in the IVC below the level of the diaphragm or a web with a collateral venous pattern. The hepatic veins are usually patent, with a high

WHVP but a normal HVPG resulting from high IVC pressure. Patients with an IVC web may be cured by surgical excision or percutaneous angioplasty.

Cardiac Disease

When pressure rises in the right chambers of the heart in constrictive pericarditis, valvular disease (e.g., mitral stenosis with tricuspid insufficiency), or cardiomyopathy of any cause, the pressure is transmitted backward through a valveless venous system from the IVC to the hepatic veins, hepatic sinusoids, and portal venous system. The consequence is a picture similar to that of hepatic vein occlusion, IVC web, or any syndrome of obstruction to the hepatic venous outflow. The symptoms of such patients —intractable ascites and hepatocellular dysfunction—may be difficult to distinguish from those associated with other causes of portal hypertension, even cirrhosis. Esophageal varices are usually not present because a gradient between the portal and azygos systems is lacking.