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CONFERENCE PROCEEDINGS

Non-cirrhotic portal hypertension versus idiopathic portal hypertension

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Abstract Portal hypertension occurs in a number of disorders other than cirrhosis and they are collectively called non-cirrhotic portal hypertension (NCPH). The common causes of NCPH include idiopathic portal hypertension (IPH), non-cirrhotic portal fibrosis (NCPF) and extrahepatic portal venous thrombosis (EHPVT). Other causes include schistosomiasis, hepatic venous outflow tract obstruction, veno-occlusive disease and congenital hepatic fibrosis. Patients with IPH and EHPVT present with upper gastrointestinal bleeding, splenomegaly, ascites after gastrointestinal bleeding, features of hypersplenism, growth retardation and jaundice due to portal biliopathy. The diagnosis is usually made by abdominal ultrasound, upper gastrointestinal endoscopy, normal liver function tests and normal liver histology. Variceal bleeding in NCPH has lower mortality as compared with cirrhosis because of better liver functions in NCPH. Treatment for NCPH includes primary prophylaxis for variceal bleeding and prevention of repeat bleeding using drugs like β-blockers, endoscopic sclerotherapy and endoscopic band ligation of varices. In patients with uncontrolled variceal bleeding or symptomatic hypersplenism, porto-systemic shunt surgery or splenectomy are required.

INTRODUCTION

Portal hypertension is generally defined as a portal vein pressure elevated above the upper normal limit of about 10 mmHg.[1,2] Elevation of portal vein pressure (PVP) occurs in a number of disorders other than cirrhosis and they are collectively called non-cirrhotic portal hypertension (NCPH). Idiopahtic portal hypertension (IPH) is just one of the NCPH. Although portal hypertension entails a serious sequela, such as variceal bleeding, mortality from variceal rupture is generally lower in non-cirrhotic portal hypertension because of a better liver function compared with cirrhosis.

The mechanism of elevation of portal vein pressure and the pathological changes causing portal hypertension vary with each disease. Portal hypertension is commonly classified according to the location of obstructive changes along the vascular system—prehepatic, intrahepatic and posthepatic—and the intrahepatic portal hypertension is further subdivided into presinusoidal and postsinusoidal one. A typical example of prehepatic portal hypertension is extrahepatic portal vein thrombosis, and Budd–Chiari syndrome due to membranous obstruction of the inferior vena cava is purely posthepatic portal hypertension.

IDIOPATHIC PORTAL HYPERTENSION (HEPATOPORTAL SCLEROSIS, NON-CIRRHOTIC PORTAL FIBROSIS)

This is an adult disease which corresponds to Banti's disease or syndrome excluding known etiologies. The disease was first described toward the end of 19th century as a disorder characterized by splenomegaly and anemia with no hematological and other causes. Subsequently, it was found that most such patients had a demonstrable etiology such as cirrhosis, schistosomiasis and portal vein thrombosis. However, when Whipple[3] analyzed 316 patients who underwent splenectomy at the Presbytarian Hospital, New York, there were 26 cases in whom no obliterative factor was found along the portal vein system. In 1962, Imanaga[4] in Japan, found that one third of his patients with portal hyper-

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tension were not cirrhotic at surgery, and had intrahepatic presinusoidal obstruction. In the same year, Ramalingaswami[5] in India, noticed that a significant proportion of autopsy livers from patients with portal hypertension had no cirrhosis, but the portal tracts were markedly fibrosed. Indian investigators coined a term non-cirrhotic portal fibrosis (NCPF) for this disease. Shortly thereafter, Mikkelsen and his group in Los Angeles (that included renowned pathologists, Edmondson and Peters)[6] described 36 patients with splenomegaly and non-cirrhotic portal hypertension in whom marked phlebosclerosis was apparent in the intra- and extrahepatic portal vein system. In more than one half of these patients the portal vein was partially or completely occluded. They called the disease hepatoportal sclerosis. It is not clear at the moment whether IPH of Japan, NCPF of India and hepatoportal sclerosis of California represent the same disorder, but clinically they are very similar.

Diagnosis

The definition adopted by the Japan IPH Study Committee (appointed by the Ministry of Health) has been 'a disorder characterized by splenomegaly, anemia and portal hypertension without demonstrable diseases'.[7] The diagnostic criteria include: (i) splenomegaly, (ii) normal to near normal liver function tests, (iii) demonstrable varices, (iv) decrease of one or more of the formed elements of blood, (v) scintiscan not typical of cirrhosis and minimal bone-marrow uptake of colloid, (vi) patent portal and hepatic veins, (vii) WHVP not as high as in cirrhosis, (viii) grossly non-cirrhotic, but frequently uneven liver surface, (ix) marked portal fibrosis with no diffuse nodule formation, and (x) elevated portal vein pressure. Although not all of these criteria are necessary, portal hypertension must be unequivocal. In advanced cases, intrahepatic portal branches are frequently occluded in the periphery as seen by portography.

Epidemiology

It is generally believed that Banti's disease was much more common in the past in Japan. When Banti first described the disease in northern Italy toward the end of the 19th century, there must have been some cases corresponding to IPH, although most of his patients had various disorders. This disorder seems to have declined in incidence since. Of the 93 cases who were splenectomized by Whipple for Banti's syndrome cited above, 17 were due to extrahepatic portal thrombosis, 50 cirrhosis or schistosomiasis and 26 were idiopathic.[3] At Los Angeles County Hospital, a leading liver center, there were 36 cases of hepatoportal sclerosis in 18 years (up to 1965).[6] That means it was very uncommon in California.

Idiopathic portal hypertension was a very common disease accounting for about 30% of patients with portal hypertension in Japan up to 1970 or so, and has been designated as one of the intractable diseases; the Government pays the medical expenses for this disease if the patient is formally diagnosed as having IPH. Taking into account this unusual situation, an epidemiological survey was carried out with the cooperation of major hospitals throughout the country. It was estimated that there were 1376 patients with IPH in 1984, and that the incidence rate was $0.75/10^6$ population with an average morbidity of 12.5 years. Thus, there was a drastic decrease in the number of IPH patients after 1970. In India where there is no indication of a decrease of NCPF, it is more common in males with a reported M:F ratio of 2:1–4:1, and an average age of 30–35 years. In Japan, middle-aged women are more commonly affected and the F:M ratio is 3:1 with an average age of 43 years (based on 624 cases).[8] In the Mikkelsen series in the USA[6] 19 were females (48.7 years) and 17 males (41.9 years). In a London series in 1981,[9] there were 16 females and 42 males with average ages of 46 and 36 years, respectively. These differences are perhaps due to the socioeconomic status of the population studied, and to differences in diagnostic criteria, whether the material was autopsy or clinical, and how strictly portal vein thrombosis was excluded, etc.

Pathophysiology

The liver is somewhat atrophic showing shrunken areas, and may have a wavy surface. The relative proportion of the left and right lobes may be grossly altered due to portal thrombosis and subsequent atrophy.[10] At autopsy, large portal vein branches may have relatively fresh thrombi. In 1974, Boyer *et al.*[11] described four cases of intrahepatic portal vein thrombosis in which the liver was studied with the vinylite-injection corrosion technique, and based on such observations, a theory has been put forward that IPH and NCPH are undiagnosed intrahepatic thrombosis. Japanese investigators question this concept because thrombosis of large intrahepatic portal branches could represent a late stage of IPH. According to Nakanuma *et al.*[12] in stage IV of IPH, large portal veins develop thrombosis. In fact, all four cases of intrahepatic portal thrombosis had portal fibrosis. The following observations[13] speak against the thrombosis theory:[11] (i) insidious onset of IPH, (ii) splenomegaly is not secondary to congestion, because splenic vein flow is increased in IPH, (iii) coagulopathy is uncommon in IPH, (iv) only three of 136 wedge biopsies from IPH patients had thrombosis (vide supra), (v) early cases have been studied by transhepatic portography and no thrombosis found, and (vi) some autopsy livers did not have gross thrombosis in the liver.

The exact cause of IPH is still obscure, but the patients have a number of immunologic abnormalities. Autoantibodies are frequently demonstrable, and an ill-defined immunologic abnormality is suspected to underlie the disease. Experimentally, portal fibrosis mimicking IPH develops following intraportal injection of killed bacteria. Occasional rheumatoid arthritis patients have splenomegaly and portal hypertension and it is possible that some IPH patients develop rheu-

matoid arthritis and are mistaken for Felty syndrom. Histologically, there is no pathognomonic changes in the spleen except for a markedly hypertrophied red pulp. In the liver, the lobular architecture is maintained, but the relationship between the portal and central areas is distorted in places. Collagen stain demonstrates irregularly distributed curly perisinusoidal fibers. The most marked changes are sclerosis of the portal vein wall which is thickened and sometimes hyalinized, and is accompanied by perivascular fibrosis. The intrahepatic portal tracts are markedly fibrosed and expanded, and the small interlobular portal vein is so narrowed that its size may not be larger than that of the atery in the same portal tract. Many aberrant vessels form around the portal tract. In peripheral portal vein branches there is diminution and devastation of small portal branches. Nayak and Ramalingaswami[14] emphasized obliterative thrombotic changes which they called 'obliterative venopathy'. However, wedge biopsy from IPH livers in Japan showed peripheral thrombosis very rarely. The irregularly distributed parenchymal atrophy is clearly due to reduced portal perfusion of the portal branch feeding that particular area; regenerative nodules of varying sizes are commonly seen. If they are small, this may be an equivalent of nodular regenerative hyperplasia, and a large regenerative nodule may form near the hepatic hilu, an equivalent of partial nodular transformation.

We studied the portal hemodynamics using Doppler ultrasound, and catheterization of the portal vein and the hepatic vein, and measured various parameters in IPH in comparison with cirrhosis patients.[7,15] Hepatic blood flow is increased, so is splenic flood flow, and the difference between WHVP and PVP is greater in IPH, the difference between WHVP and FHVP is greater in cirrhosis, presinusoidal resistance is greater in IPH and postsinusoidal resistance is greater in cirrhosis, and cirrhosis has more intrahepatic shunt circulation. Thus, the site of portal resistance is mainly presinusoidal, but postsinusoidal resistance is just as high as presinusoidal resistance in IPH, whereas in cirrhosis postsinusoidal resistance is 10 times the presinusoidal resistance.

Clinical features

The most common clinical presentation is hematemesis, an incidentally found splenomegaly, anemia, and complaints associated with anemia. Physical examination demonstrates a large spleen and signs of anemia. Laboratory studies show pancytopenia compatible with hypersplenism. The weight of the spleen varies from 150 g to 2 kg with an average of 723 g in Japan.[10] Colloid scintigraphy demonstrates a large spleen and a near normal liver with no bone-marrow uptake. Portography shows an enlarged portal vein axis with no thrombus, and poor opacification of peripheral portal branches, suggesting narrowing or occlusion. Venograms are unique in that the branches run smoothly with frequent vein-to-vein anastomoses. These venogram features are perhaps due to parenchymal atrophy. The hepatic arteries are small while the splenic artery is markedly enlarged and winding in its course, frequently forming an aneurysm at the splenic hilum.

Immunological studies of IPH have shown that a significant proportion of patients are positive for various autoantibodies, and less frequently have a coexistent autoimmune disease, such as thyroiditis, systemic lupus erythematosus, Sjögren's syndrome; the test for lupus anticoagulant is negative.[13] There is no evidence of coagulation factor deficiency or a hypercoagulable state. Hepatitis B and C are not etiologically associated.

Treatment and prognosis

The liver slowly undergoes atrophy which is not necessarily progressive, and the liver functional reserve is well maintained. The major cause of death is variceal bleeding. In rare instances, repeated uncontrollable bleeding may induce hepatic insufficiency. The survival curve for IPH patients is somewhat between that for cirrhosis and for a healthy population of a comparable age. Management and prophylaxis of variceal bleeding are no different from those for cirrhotic patients. Because liver function is good, the risk of operative death is practically nil, and some surgeons carry out a prophylactic operation for portal decompression or devascularization such as esophageal transection and Hassab operation. However, there has been no randomized prospective study on the efficacy of prophylactic surgery or sclerotherapy in IPH.

EXTRAHEPATIC PORTAL VEIN OBSTRUCTION

Definition, epidemiology and pathophysiology

Extrahepatic portal vein obstruction (EHO) is conventionally defined as obstruction in the prehepatic portion of the portal vein. The portal and splenic veins are continuous, but thrombosis within the splenic vein not occluding the portal trunk is not included. Splenic vein thrombosis is caused by a pancreatic disease or associated with abdominal surgery such as splenectomy and other abnormalities within the abdomen. The thrombus in the splenic vein or superior mesenteric vein may extend into the portal vein. Portal vein thrombosis is a common complication of liver cirrhosis, but it usually lacks a distinct clinical sign and is not included in EHO. Difficulty arises when the first order portal veins are occluded at the porta hepatis while the portal trunk is patent. By definition it should not be diagnosed as EHO, but its pathophysiology is the same and should be treated as EHO.

Extrahepatic portal vein obstruction is a relatively uncommon disease in Western countries. Webb and Sherlock[16] documented 97 cases seen in 18 years up to 1970 at the Royal Free Hospital, London. Thus, a major liver center of the world sees several cases per year. By contrast, EHO is very common in India. At the All India Institute Medical Sciences, 87 cases of EHO

and 83 cases of NCPF were treated in 6 years. In Chandigarh, 100 cases of EHO and 38 cases of NCPF were seen in an unspecified period.[17] In Japan, EHO is less common than IPH. The incidence of EHO among 24 7728 autopsies performed in 1975–1982 was 0.055%. The IPH Study Group of Japan studied 184 surgically and angiographically confirmed cases of EHO in comparison with 469 cases of IPH.[18] It was found that epidemiology is clearly different, but both have similar clinicopathological features. The age distribution demonstrated two peaks. There were more cases in the first decade, and another peak in the 5th decade. The number of cases below age 20 was about the same as that above age 20. There were slightly more males (M:F ratio, 1.2:1). In India, the majority of EHO cases are below age 25, and only very few are above age 40.

There are many etiologic factors, and the cause of EHO varies with the patient. Studies in children with EHO have found frequent histories of umbilical sepsis and other infections, however; catheterization for umbilical exchange transfusion does not seem to cause portal thrombosis frequently. In adults, the reported etiologies include intra-abdominal sepsis, biliary tract disease, pancreatitis, appendicitis, pylephlebitis, duodenal ulcer, subacute bacterial endocarditis, postoperative infection, abdominal wound, hypercoagulable diseases such as polycythemia, and coagulation factor deficiency. Although about half of young EHO patients had no history that might cause portal thrombosis (so-called idiopathic), many of them could have had some infections not diagnosed at the time.

Liver pathology is not very characteristic. At operation for portal decompression or devascularization, the liver looks grossly normal. Histologically, in about 40% of adult cases there is portal fibrosis, but fibrosis is minimal or absent in children. If the intrahepatic portal branches are thrombosed, they are organized, recanalized and the cut section looks like a sponge. It is not clear whether some of the adult EHO cases with severe portal fibrosis in Japan are similar to the hepatoportal sclerosis cases in Mikkelsen's series who had portal thrombosis. The spleen is enlarged, but the weight is about two-thirds of the IPH spleen. In EHO, PVP is the pressure measured in the portal vein upstream from the obstruction. WHVP is low, and clearly the portal obstruction or resistance is presinusoidal, and most likely prehepatic. Portal vein pressure in EHO is somewhat higher but WHVP lower compared with IPH, hence a greater difference (PVP-WHVP).

Clinical features and diagnosis

The presenting symptoms and signs are hematemesis, splenomegaly noted as an abdominal mass, anemia, abdominal distension due to ascites, and abdominal venous dilatation. Unlike IPH, hematological changes are very mild if present. Liver function tests are only minimally abnormal. Esophageal varices are found in 90% of patients, and gastric varices in 36%. Occlusion of the portal vein has to be demonstrated by ultrasound and more accurately by portography. In our survey, the portal vein including the porta hepatis alone was occluded in 71.5%, portal and superior mesenteric veins in 2.5%, portal and splenic veins in 13.6%, portal, superior mesenteric and splenic veins in 10.1%, and portal and other veins in 2.5%.

A fresh thrombus within the portal vein can be identified by ultrasound as an echogenic material within the lumen. Blood flow should then be studied by Doppler ultrasound in and around the thrombus. If it is a complete block, no flow signal will be obtained, and if incomplete or mural thrombosis, some flow signal will be obtained. A portogram is desirable for diagnosis, but non-surgical direct portography is difficult technically.

Cavernous transformation

Portal obstruction is followed by formation of the so-called cavernous transformation. It is a hepatopetal collateral route consisting of many winding thin veins readily identified by ultrasound as an irregular vascular structure near the hepatic hilum. The mechanism of cavernous transformation remains an enigma. It is a venous neovascularization to compensate for the lack of portal venous flow into the liver. These thin veins enter the liver and then join patent intrahepatic portal branches at various levels, depending upon the sizes of portal branches that were thrombosed. Cavernous transformation may be identified by superior mesenteric arterial portography, and can also be indirectly suspected from a markedly widened hilar portal area on computed tomography (CT). It develops even if the portal obstruction is incomplete whenever portal venous flow is reduced beyond a critical level. The time required to form cavernous transformation was estimated in patients with hepatocellular carcinoma in whom the cancer invaded the portal trunk; it was only several weeks.[19]

Treatment and prognosis

Management of variceal bleeding and encephalopathy is no different from that in cirrhosis and other portal hypertensive diseases. The most serious complication is thrombosis of the superior mesenteric vein which may cause bowel infarction that requires an urgent surgery. Because the liver function is good, mortality from bleeding and encephalopathy is generally low, yet there are some fatalities from such complications. Incomplete portal obstruction or a web may be corrected by percutaneous transhepatic angioplasty. In the London series,[16] 24 of 97 patients (25%) died between 3 weeks and 20 years with an average survival of 10 years. Although disputed, prophylactic surgery for portal hypertension has been successful in Japan where the 10-year survival rate was 100% in 25 patients who underwent prophylactic surgery.

SCHISTOSOMIASIS (BILHARZIASIS)

Epidemiology

Of the three cardinal *Schistosoma* species, *S japonicum*, *S mansoni* and *S hematobium*, the first two are known to cause liver disease. *Schistosoma hematobium* mainly affects the urinary tract, but in an advanced stage, the liver also develops portal fibrosis. *Schistosoma japonicum* is capable of producing far more ova than *S mansoni*, hence more severe liver disease. It is widely distributed throughout the world, particularly in the Asia. *Schistosomiasis japonica* was once called Katayama disease because it was studied extensively in Japan, but it has since been eradicated. In China, it had been estimated that about 100 million people were infected. During the Mao regime, all-out efforts were made to eradicate the disease. The campaign was partially successful, and the number of patients has clearly decreased, but there still are some patients with chronic schistosomiasis. *Schistosoma mansoni* is endemic in lower Egypt, in most parts of Africa, Middle East and South America. In Brazil alone, about 4.5 million people are infected.

The infection occurs when the cercariae enter the body through the skin, and adult worms eventually inhabit tributaries of the inferior (*mansoni*) or superior (*japonicum*) mesenteric veins. They lay several hundred to thousand eggs per day for several years, then cease egg production, and the life span is 10–30 years. The ova that have flowed into portal venules and got stuck in the portal tract incite inflammation which is followed by marked fibrosis.

Pathophysiology

The transition from acute to chronic schistosomiasis is insidious. The inflammatory reactions due to the ova deposited in the portal venules eventually lead to portal fibrosis. The hepatic venules are not affected in the early stage, and the portal resistance is mainly presinusoidal. As the changes in the portal tracts advance, lobular distortion, destruction of portal venules and intrahepatic collateral formation occur, and hepatic veins are affected due to circulatory disturbance as evident from WHVP in advanced cases. Due to tissue collapse, the liver surface becomes grossly uneven with bosselated areas and furrows, and the liver comes to look like a turtle shell in the case of schistosomiasis japonica. The portal vein may develop inflammation with a heavy egg load, and the vein wall may eventually calcify. A small percentage of patients with chronic schistosomiasis develops huge splenomegaly. Again, splenomegaly does not reflect the degree of portal hypertension, but is perhaps induced by an unknown diathesis of the person. During the clinical follow-up splenomegaly develops within a relative short period of time as observed among the Japanese patients with schistosomiasis. The distribution of portal fibrosis is not homogeneous and disfigurement of the liver seems to be related to the distribution of the worms within portal venules. More often, the lower anterolateral area of the right lobe undergoes severe atrophy, and on colloid scintigraphy, the liver assumes an inverted triangle configuration. Hepatic fibrosis is different to cirrhosis, but the expression 'cirrhosis' has often been used for markedly disfigured livers. Severe gross change of the liver is uncommon in *S mansoni*, and rather the large portal tract expands with fibrosis to assume a picture called 'clay pipe-stem fibrosis'.

Clinical features and diagnosis

The acute stage mimics acute bacterial infection. As the disease turns chronic and the liver develops portal fibrosis, esophageal varices, splenomegaly and other signs of portal hypertension emerge. Many patients with mild fibrosis remain asymptomatic. Even if the patient bleeds from esophageal varices, the liver function is usually good and the patient will survive if treated properly.

Laboratory studies will show various grades of hypersplenism or reduced blood cells. Encephalopathy is uncommon without a precipitating factor, and so is ascites. If the disease is very severe, a decompensated state of the liver may develop with muscle wasting, hypoalbuminemia and chronic ascites. Other coexisting factors, such as hepatitis B virus infection and alcoholism, may aggravate the clinical conditions and change the natural history. In the case of schistosomiasis mansoni, extrahepatic manifestations have been described such as pneumonia caused by dead worms after chemotherapy, and a mass formation along the colon.

Definitive diagnosis is made by the demonstration of schistosomal ova. It is done by biopsy of the rectal mucosa or the liver. Because the worms concentrate more densely in the distal colon, rectal mucosa always has abundant ova.

Various immunological diagnostic methods have been proposed and are in use. An enzyme-linked immunoadsorbent assay (ELISA) and enzyme-linked-immunoelectrodiffusion assay (ELIEDA) have been used for schistosomiasis mansoni. For schistosomiasis japonica, circumoval precipitin test (COPT) seems to be the most reliable. Radiological examination using modern imaging techniques is also useful. A liver with advanced schistosomiasis is recognized by ultrasound from irregular hyperechoic bands, and calcified portal tracts are seen on plain CT. The liver configuration may change to an inverted triangle on colloid scintigraphy as discussed. Liver histology shows numerous ova in the portal tract, and they are calcified if the disease is old.

Treatment

Praziquantel and oxamniquine are currently used for eradication of the worms in the acute stage of the disease. The cure rate with oxaminiquine is 80% in adults and 65% in children. Even if it does not kill all the worms, there will be a sharp reduction in egg laying. In chronic patients, the worms no longer lay eggs and the patient may not require specific treatment. The eggs die

within several weeks and the interior of the egg is lost or undergoes calcification. In patients who have bled, an elective measure for the prevention of rebleeding may be indicated, as in liver cirrhosis.

OBSTRUCTION OF THE HEPATIC VEINS

Obstruction of the hepatic vein or a blockage in the hepatic venous outflow is mainly caused by hepatic vein thrombosis and compression by a space occupying expanding lesion. It is generally called Budd–Chiari syndrome, but the definition is not well established. In hepatic vein thrombosis, the ostia of the major hepatic veins are often involved and the disease may be confused with an idiopathic type of Budd–Chiari syndrome in which the hepatic portion of the inferior vena cava (IVC) is the primary site of thrombosis. For the latter, this author is suggesting the term 'obliterative hepatocavopathy'.[20,21]

Etiology and epidemiology

Malignant tumors may cause incomplete or complete obstruction of major hepatic veins, but it is relatively uncommon. They more often invade the IVC first then the hepatic vein. The reports include hepatocellular carcinoma, renal cell carcinoma, Wilm's tumor, adrenal carcinoma and leiomyosarcoma of IVC. In an Indian series, it occurred in 11 (8.9%) of 123 Budd-Chiari cases excluding primary IVC obstruction. In the regions of the world where hydatid disease is endemic, hepatic vein obstruction by echinococcosis is not very rare. An enlarging cyst caused by *Echinococcus granulosa* may compress upon the hepatic vein, and *E multilocularis* may directly invade a large hepatic vein to cause obstruction. A liver abscess itself may not obstruct the hepatic vein, but extending pyogenic inflammation induces thrombosis within a large vein. Hepatocellular carcinoma is known to invade into the hepatic vein, sometimes further into the IVC and right atrium, but in such cases, typical clinical presentation is masked because the liver is already markedly invaded by the cancer with severe clinical manifestations. Thus, infectious and parasitic etiologies show a geographic distribution with a large difference between developing and developed countries.

Hepatic vein thrombosis

There are often underlying thrombogenic conditions of which primary myeloproliferative disorders are the most common in Western countries. According to Valla,[23] there are just as many latent cases of myeloproliferative disorder as full-blown polycythemia vera. The latent cases may be diagnosed by a bone-marrow culture and demonstration of erythroid colony formation. Other hypercoagulable conditions include oral contraceptive use, paroxysmal nocturnal hemoglobinuria, lupus anticoagulant and anticardiolipin antibodies, pregnancy and puerperium. In India, pregnancy and puerperium associated hepatic vein theombosis is often fulminant and the major cause of fatality.[24] Vasculitis as a manifestation of collagen disease may cause hepatic vein thrombosis, such as Beçhet disease, sarcoidosis, and immunoallergic vasculitis. In most studies, a considerable proportion of the cases were idiopathic, but in the French series, nearly 90% of the patients had demonstrable underlying or etiologically associated disorder.[25]

Pathophysiology

A large part of the hepatic vein outflow tract must be occluded for clinical symptoms to develop. Patients with only one of the three major hepatic veins occluded may remain asymptomatic. Pressure increases in the sinusoids that drain into the affected vein and the flow within the upstream lobules decreases. Increased sinusoidal pressure causes sinusoidal dilatation and congestion, as reflected by hepatomegaly. Increased sinusoidal pressure increases hepatic lymph, and when the increase surpasses the capacity of the lymphatic drain, fluid of a high protein content leaks through the liver surface. However, in an actual patient with hepatic vein thrombosis, ascites does not have such a high protein level, perhaps due to changes in the permeability of the sinusoid wall and dilution by a low protein fluid coming from the mesentery.

Besides the three major hepatic veins, the liver has one vein caudal to them—the inferior right hepatic. In nearly one-half of patients, this vein is not affected in the first attack, and the flow within this vein markedly increases compensating for the lack of flow in the other veins, resulting in a marked enlargement of the caudate lobe. There is a gross disfigurement readily seen by ultrasound and CT, and upon injection of radiocolloid, the activity concentrates in the enlarged caudate lobe (central concentration of radioactivity).

Following thrombosis, the blood coming from the hepatic artery has to leave the liver and small and large collateral channels develop between the obstructed areas and the areas of the liver where veins are patent, or the parietal and diaphragmatic veins. The pattern of collateral route formation varies greatly with each patient, with intra- and extrahepatic collaterals eventually going into the hemiazygos and azygos, retrograde flow within the portal vein, etc. Centrilobular congestion and ischemia cause centrilobular necrosis. Hepatic failure may ensue depending upon the extent of thrombosis and acuteness of obstruction. It could be fulminant. Centrilobular necrosis is soon followed by fibrosis, and within a relatively short period compensatory regeneration becomes recognizable as a nodule formation. The liver eventually develops congestive cirrhosis in which the spatial relationship between the portal tract and central vein is reversed from that in conventional cirrhosis. Hemodynamically, WHVP and intrahepatic sinusoidal pressure are elevated, and so is FHVP, making hepatic vein pressure gradient very low.

Clinical features and diagnosis

The patient with acute hepatic vein thrombosis typically presents with ascites, abdominal pain and liver enlargement. Other common signs include splenomegaly, edema, jaundice and fever. Hepatic encephalopathy and gastrointestinal bleeding are less common. In a fulminant form which is rare, hepatic failure sets in within a few days with marked aminotransferasemia and renal failure. The severity depends on the number of veins involved. Some patients will present as a chronic disease with less prominent signs, such as progressive ascites and low grade aminotransferasemia, but these patients if left without treatment may develop slowly progressive hepatic failure or gastrointestinal bleeding. Ascites is resistant to therapy and very annoying for the patient. In a recent French experience the three year survival rate was 50%.[25]

Diagnosis

Abdominal ultrasound will readily demonstrate hepatic vein thrombosis as an echogenic material within the lumen of one or more of the hepatic veins. An enlarged caudate lobe may also be recognized. Injection of contrast medium will show in the early phase its concentration in the center of the liver or over the caudate lobe. Space occupying lesions as the cause of hepatic vein obstruction is readily found by CT and ultrasound. Magnetic resonance imaging is about the same as CT in its diagnostic capability. If the inferior right hepatic vein is patent, radiocolloid scintigraphy will show central concentration as already described. Liver biopsy is not necessary for the diagnosis because imaging techniques suffice for diagnosis, but it may provide in chronic cases histological information on the severity of hepatic fibrosis and cirrhosis. Diagnosis of hepatic vein obstruction may be difficult from biopsy alone in some of the chronic cases because the liver only shows fibrosis without evidence for centrilobular congestion.

Treatment

In an acute case, further thrombosis has to be prevented with heparin and a vitamin K antagonist. If the diagnosis was made in a very early stage of hepatic vein thrombosis, one can place a catheter in the affected hepatic vein through the vena cava and infuse a thrombolytic agent, such as tissue plasminogen activator (TPA), but its efficacy is uncertain. In a situation in which only the opening of the hepatic vein into IVC is closed as a membrane or a short segment occlusion, transhepatic or surgical angioplasty is possible. Dorsocranial liver resection and direct hepatoatrial anastomosis has been attempted. The surgical approach largely depends on the status of IVC and the portal vein. In the absence of obstruction in the IVC and portal vein, side-to-side portocaval shunt or mesocaval shunt is the choice. Liver transplantation is indicated in fulminant patients and in those who have developed severe cirrhosis. Otherwise, portacaval shunt is just as effective as liver transplantation.

INFERIOR VENA CAVA OBSTRUCTION (OBLITERATIVE HEPATOCAVOPATHY)

This disease corresponds to membranous obstruction of the inferior vena cava (MOVC) which was included in the Budd–Chiari syndrome. However, primary lesion in this disease occurs in the hepatic portion of the inferior vena cava (IVC). The etiology is unknown, but the disease is endemic in certain developing countries such as Nepal, China, India and among southern African blacks. The disease should be treated separately from classical Budd–Chiari syndrome. Thrombosis occurring at the level of the diaphragm frequently occludes the ostia of major hepatic veins and cause hepatic vein outflow obstruction. Thus, the pathophysiology of this disease is practically the same as that of classical Budd–Chiari syndrome. The thrombus organizes and turns into a fibrous tissue obstructing IVC. It has been called membranous obstruction, but more often it is thicker than a membrane.

Epidemiology

This disease is common in developing countries. By contrast, when Mitchell *et al.* analyzed 253 cases of Budd–Chiari syndrome in the English literature they found only three reports of MOVC found between 1960 and 1980.[26] Membranous obstruction of the inferior vena cava was not too uncommon in Japan. In 1968, Nakamura *et al.*[27] collected 90 autopsy cases of Budd–Chiari syndrome of which 71 were with no known etiology: seven were classical type with hepatic vein thrombosis within the liver, 72% had obstructive lesions both in IVC and hepatic vein ostia, and 18% in IVC only. They also noted that 41% of these 71 cases had a complicating HCC. When our national group for the study of aberrant portal hemodynamics studied 157 authentic cases of Budd–Chiari syndrome, only 5.7% were of the classical type and the remainder had obliterative hepatocavopathy, mostly with involvement of the hepatic vein ostia.[28] At the liver center of Bir Hospital, Kathmandu, Nepal, there were 150 cases of IVC thrombosis which constituted approximately one-fifth of all patients with chronic liver disease, and all were idiopathic.[29] Wang[30] operated on 430 cases of Budd–Chiari syndrome in Beijing which included only seven cases of hepatic vein thrombosis. Thus, the vast majority of hepatic vein outflow block is IVC thrombosis in these countries. A study in Chandigarh, India,[22] analyzed 177 cases of Budd–Chiari syndrome of which 64% were idiopathic or MOVC. In 1982, Simson from Pretoria, South Africa, reported on the frequent complicating HCC (47%) among 101 black cases of MOVC.[31] These primary IVC obstruction or thrombosis cases are much more prevalent in developing countries than developed countries. The frequency of

complicating HCC varies with the country. It is very high among African blacks, but is much less elsewhere. It was 6.4% among 157 cases of Budd–Chiari syndrome in 10 years in Japan.

Pathophysiology, clinical features and diagnosis

The cause of MOVC was thought by some to be a congenital vascular malformation. However, this is an adult disease with the peak age in the sixth decade in Japan. If this were a congenital malformation, the patient should present with ascites, hepatomegaly and venous dilatation shortly after birth. In our study of 17 autopsy cases of Budd–Chiari syndrome, there was only one case of classical Budd–Chiari syndrome with unobstructed IVC. The remainder had a thick or thin IVC obstruction with and without fresh thrombosis. Histological examination of the membrane showed that it was an organized thrombus, with a normal IVC wall structure beneath it. The etiology IVC thrombosis is not known at the moment. For some reason, the hepatic portion of IVC is predisposed to thrombosis. Some investigators theorized that the diaphragmatic movements for respiration and coughing induce microscopic injuries to the endothelium of IVC which invite thrombosis. From my own experience in Nepal where most patients have fever with occasional positive blood cultures, bacterial infection is one of possible causes.

The clinical presentation is virtually the same as that of classical Budd–Chiari syndrome, but is generally less severe, because the three veins are seldom occluded simultaneously and completely. Dilatation of subcutaneous veins over the body trunk is much more prominent compared with hepatic vein thrombosis. Abdominal pain, ascites and hepatomegaly, particularly enlargement of the caudate lobe, are prominent, but most patients sustain the acute episode. They will subsequently have repeated episodes of varying severity at variable intervals, and go into a chronic state. Liver histology shows centrilobular congestion and bleeding in the acute stage, but as the disease turns chronic, congestive findings become less prominent with increasing fibrosis. Signs of portal hypertension, such as esophageal varices, splenomegaly, and dilatation of abdominal collateral veins become more evident, and the liver will eventually turns into congestive cirrhosis. Repeated episodes of the symptoms are perhaps due to new thrombosis occurring at the same level of IVC.

Diagnosis is the demonstration of thrombosis or occlusion of IVC by ultrasound and perhaps MR imaging. Such imaging diagnosis will delineate intrahepatic collaterals and collaterals veins that originate in IVC and run cephalad along the vertebral column. The portal vein flow is usually antegrade.

Treatment

If the obstructive lesion is thin, angioplasty may be carried out. For the IVC membrane, several balloon catheters are passed from the femoral veins to perforate the membrane, and the hole is dilated. For a thin hepatic vein occlusion, transhepatic angioplasty may be performed. If these procedures are not applicable or have failed, surgical angioplasty may be carried out. Other options include mesocarval anastomosis, shunting between IVC and right atrium, between IVC and the right subclavian vein, and cranial hepatic resection and hepatoatrial anastomosis.

VENOOCCLUSIVE DISEASE

In Jamaica, approximately one third of cirrhosis seen at autopsy is a non-portal fibrosis with occlusion of centrilobular veins and centrilobular fibrosis. Most these patients are young. The onset is often acute with jaundice, hepatomegaly and ascites. Varices and variceal bleeding are the prominent clinical features. This is a toxic injury of the liver histologically manifested by centrilobular necrosis and congestion. It is believed that the disease in Jamaica is caused by pyrrolizidine alkaloids of *Senecio* and *Crotalania* plants contained in natural 'bush-tea' drunk by some local residents. These alkaloids produce similar lesions in animals. This disease is extremely uncommon in Japan where there has been only one case ever reported. There was an outbreak of a similar disease in north-west India in 1974 in which one whole farming village was affected with a 10% mortality, and all affected dogs died with ascites. Although the investigators failed to identify the offending toxin, ingestion of moldy maize was thought to be related to this epidemic of toxic liver disease which mimicked venoocclusive disease (VOD).

Similar lesions are seen after bone marrow transplantation in patients who received alkylating agents as preparation for transplantation. This incidence ranges from 7 to 50%. It also occurs after radiation to the liver. Clearly, VOD is caused not only by bush-tea alkaloids, but by a number of organic compounds. Centrilobular damage is followed by thrombotic occlusion and thrombosis may extend towards larger hepatic vein branches, but portal hemodynamic changes that ensue are not well characterized. Diagnosis is made by liver biopsy. No splecific imaging feature is known.

SARCOIDOSIS

The liver is involved histologically in 17–90% of the cases of sarcoidosis depending on the report, but clinical manifestations of the liver disease is uncommon. In a series of 300 cases, there was clinical and/or biochemical evidence of liver disease in 20. The granulomas occur in any area of the liver, but are more frequent in the portal tracts causing injury to the portal veins. Portal hypertension which is rather uncommon, is presinusoidal in the early phase of the disease caused by the pressure due to granulomas, but in advanced cases with marked fibrosis, there will be sinusoidal obstruction to portal blood flow as well. In some patients, signs of portal hypertension may be the presenting symptom.

CONGENITAL HEPATIC FIBROSIS

This is a form of autosomal recessive polycystic kidney disease which is generally divided into several types according to the age of onset. Of these, the ones presenting in childhood and adolescence are frequently associated with portal hypertension beside kidney disease. Infants present with abdominal distension from enlarged organs, respiratory distress and hypertension. Young adults seek medical attention because of variceal bleeding or hepatosplenomegaly. Liver function is good but portal hypertension is prominent. The liver is enlarged and firm, with a fine reticular pattern of portal fibrosis. No cysts are grossly recognized. Microscopically, there is diffuse periportal fibrosis varying in thickness. The fibrous bands encircle single lobules or a group of them. There are numerous uniform small bile ducts and an interrupted circular arrangement of the ducts (ductal plate malformation within the fibrous band). The portal hemodynamic changes vary with the report. In one study one patient demonstrated a considerable gradient between PVP and WHVP, whereas another report in which six patients were investigated did not show increased presinusoidal resistance. Diagnosis largely depends on liver histology, and no specific imaging feature is known.

HEMATOLOGIC DISORDERS

Myeloproliferative disease, agnogenic myeloid metaplasia, and certain other hematologic disorders are known to cause portal hypertension. They include leukemia, lymphoma, mastocytosis, Gaucher' disease, and osteopetrosis. It is mainly presinusoidal and partially sinusoidal. It has been generally thought that portal hypertension is due to increased hepatic blood flow, and infiltration of malignant and hemopoietic cells within the sinusoids. More recently, however, Wanless emphasized portal vascular changes and thrombosis as the cause of portal hypertension. More studies are needed for the exact cause of portal hypertension.

NODULAR REGENERATIVE HYPERPLASIA AND PARTIAL NODULAR TRANSFORMATION

Both nodular regenerative hyperplasia and partial nodular transformation are rare disorders of poorly understood etiologies. In the former, 1–2 mm nodules of regenerating hepatocytes occur rather diffusely compressing the intervening liver parenchyma. There is no fibrosis surrounding the nodules. Partial nodular transformation was originally described by Sherlock *et al.*[32] in patients with portal hypertension in whom the liver had a large regenerative nodule near the hepatic hilum. Similar nodules are seen in idiopathic portal hypertension. According to Wanless[33] such nodules are a result of portal circulation disturbances. Nodules form in the area of the liver where there is adequate portal erfusion in compensation for the parenchymal atrophy caused by decreased portal perfusion as a result of vascular changes. Therefore, these nodules are compensatory histological changes and do not represent disease entities.

CHEMICALLY INDUCED NON-CIRRHOTIC PORTAL HYPERTENSION

A number of chemicals, drugs and organic compounds are known to cause portal hypertension. Of these, arsenic-induced portal hypertension is perhaps the most frequently described followed by vinyl chloride monomer, vitamin A (hypervitaminosis), mercaptopurine, thioguanine, azathioprine, busulfan, and chlorambucil. Portal fibrosis, perisinusodial fibrosis, portal venular injury and other histological changes are described.

ARTERIOPORTAL COMMUNICATIONS IN THE SPLANCHNIC BED

Communication between the artery and the portal vein system can occur under various conditions leading to flow of arterial blood into the portal vein, producing portal hypertension. The most common cause of arterioportal fistula is trauma, and other causes include rupture of an aneurysm, diagnostic punctures of the liver (biopsy, catheterization) and congenital arteriovenous fistula. If the communication is small in diameter, no portal hypertension results. According to Reynolds[2] forcibly increased portal blood flow following a wound induces hepatoportal sclerosis which subsequently reduces the once increased portal inflow. Thus, increased portal venous flow will induce portal hypertension and portal sclerosis.

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