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TOPIC HIGHLIGHT

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Budd-Chiari syndrome: Etiology, pathogenesis and diagnosis

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Abstract

Budd-Chiari syndrome is a congestive hepatopathy caused by blockage of hepatic veins. This syndrome occurs in 1/100 000 in the general population. Hypercoagulable state could be identified in 75% of the patients; more than one etiologic factor may play a role in 25% of the patients. Primary myeloproliferative diseases are the leading cause of the disease. Two of the hepatic veins must be blocked for clinically evident disease. Liver congestion and hypoxic damage of hepatocytes eventually result in predominantly centrilobular fibrosis. Doppler ultrasonography of the liver should be the initial diagnostic procedure. Hepatic venography is the reference procedure if required. Additionally liver biopsy may be helpful for differential diagnosis. The prognosis of the chronic form is acceptable compared to other chronic liver diseases.

Key words: Budd-Chiari syndrome; Etiology; Pathogenesis; Diagnosis

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INTRODUCTION

Budd-Chiari syndrome (BCS) is an uncommon disorder characterized by obstruction of hepatic venous outflow. The obstruction may be thrombotic or non-thrombotic anywhere along the venous course from the hepatic venules to junction of the inferior vena cava (IVC) to the right atrium. Hepatic veno-occlusive disease and cardiac disorders are excluded from this definition. BCS is a heterogeneous clinical condition-it may be curable or potentially lethal. The patients have an acceptable prognosis with appropriate management compared to other chronic liver diseases. It is a rare but important syndrome because many disorders, such as hematologic or malignant diseases, may be complicated with BCS.

George Budd, a British internist, described three cases of hepatic vein thrombosis due to abscess-induced phlebitis in 1845, and Hans Chiari, an Austrian pathologist, added the first pathologic description of a liver with "obliterating endophlebitis of the hepatic veins" in 1899.

BCS occurs in 1/100 000 of the general population worldwide[1]. Patients may present with acute signs and symptoms of abdominal pain, ascites and hepatomegaly or more chronic symptoms related to long-standing portal hypertension.

Some authors suggest that IVC thrombosis is a distinct entity, named as obliterative hepatocavopathy. Primary membranous obstruction of the IVC is a sequela of IVC thrombosis without hepatic vein thrombosis, and is more common in the Far East, accounting for 60% of BCS patients in Asia[2]. Although etiologies are similar, IVC thrombosis has an indolent course and is complicated more commonly with hepatocellular carcinoma.

ETIOLOGY

BCS is considered primary or secondary depending on the origin of the obstructive lesion. If obstruction is the result of endoluminal venous lesion-like thrombosis, primary BCS is considered. In secondary BCS, the cause originates from neighboring structures like extrinsic compression or tumor invasion.

Thrombosis is the major cause of hepatic vein obstruction. The combination of one or more thrombogenic disorders and a triggering factor is necessary for venous thrombosis, particularly hepatic vein thrombosis. Most patients with BCS have an underlying condition that predisposes to blood clotting. Obstruction is mainly caused by primary intravascular thrombosis. At least one hereditary or acquired hypercoagulable state could be identified in 75% of patients; more than one etiologic factor may play a role in 25% of patients[3]. A predisposing disorder may appear later than the diagnosis of BCS.

Primary myeloproliferative diseases are the leading cause of hepatic vein thrombosis, and are diagnosed in 20% of cases[4]. The prevalence reaches 45% to 53% when occult or latent myeloproliferative disorders are included[5]. Symptomatic hepatic vein thrombosis has been reported in

1% of patients with primary myeloproliferative disorder[6]. Spontaneous erythroid colony formation is accepted as a clue of myeloproliferative disorder. In these patients with occult myeloproliferative disease, peripheral blood changes are not characteristic, but a particular anomaly of bone marrow progenitor cells-spontaneous erythroid colony formation-could be detected. In idiopathic BCS patients, it may be seen in up to 87%, suggesting that the majority of BCS patients have myeloproliferative disease, which is not apparent at that time[7,8]. Necropsy studies showed a 6% incidence of hepatic vein thrombosis in individuals with polycythemia vera or agnogenic myeloid metaplasia[9]. Polycythemia vera accounts for 10%-40% of cases. Essential thrombocythemia and myelofibrosis are less prevalent causes.

Factor V Leiden leads to resistance to activated protein C. In Western countries, factor V Leiden and factor Ⅱ gene mutation are found in about 25% and 5% of BCS patients, respectively[4,10]. BCS is associated with heterozygosity for both factor V Leiden and the G20210A mutation of the prothrombin gene and methylene tetrahydrofolate reductase mutation. Factor V Leiden is present in a majority of pregnancy- or oral contraceptive-related cases[10]. Anticardiolipin antibodies are found in about 25% of cases[11]. Hyperhomocysteinemia is also a risk factor for BCS.

Levels of protein C, protein S, and antithrombin Ⅲ may also be low in the presence of an acute thrombus and in patients with liver disease, including BCS. Because these circulating proteins are synthesized in the liver and are affected in liver dysfunction, proof of the primary deficiency as the cause is difficult. Familial studies are needed for a definitive conclusion. Primary protein C deficiency is the most common disorder in this group, with a prevalence of about 25%[10].

The use of oral contraceptives is a risk factor for BCS (particularly high-estrogen-content pills), with an approximate factor of 2.37[12]. Hepatic vein thrombosis has been described both in pregnancy and in the immediate postpartum period. Many patients in whom BCS develops in association with the use of oral contraceptives or pregnancy may also have an underlying thrombophilia, either inherited or acquired[13].

Hepatic vein thrombosis is seen in up to 12% of patients with paroxysmal nocturnal hemoglobinuria and is the main cause of mortality in this disorder. Hemoglobinuria may be absent at the time of occurrence or diagnosis of thrombosis[13,14].

Behcet's disease accounts for less than 5% of cases. In a series of 493 Turkish patients with Behcet's disease, large vein thrombosis was documented in 10.8% (53 patients) and 26.4% of them were hepatic vein thrombosis[15]. Hepatic vein thrombosis in Behcet's disease is likely secondary to IVC thrombosis[16]. IVC thrombosis was reported in 8 of 14 patients in a Turkish study of hepatic vein thrombosis secondary to Behcet's disease[15].

Abdominal trauma, ulcerative colitis or celiac disease may be a cause of BCS combined with underlying thrombophilias. Several case reports have described granulomatous involvement of the hepatic veins, either idiopathic or related to sarcoidosis.

In most cases, the local factor leading to the occurrence of thrombosis in hepatic veins cannot be determined. However, the predisposing factor could be recognized in more than 90% of cases with proper investigations. In theory, the remaining cases have unknown thrombogenic disorders which play a role in thrombosis.

Compression caused by tumors of adjacent organs or polycystic kidney disease may cause BCS. Parasitic liver diseases like hydatid cyst or amebic liver abscess are rare etiologic factors in secondary BCS. Cases of BCS secondary to pyogenic liver abscess have also been reported in the literature[17].

PATHOGENESIS

Blockage of two or more major hepatic veins increases the sinusoidal pressure and reduces sinusoidal blood flow. Obstruction of a single hepatic vein is generally not evident; two veins must be blocked for clinical disease. The result of these hemodynamic changes is sinusoidal dilation and filtration of interstitial fluid. Filtrated interstitial fluid passes through the liver capsule when it exceeds the capacity of lymphatic drainage[18,19]. Thus, liver congestion, right upper quadrant pain and ascites occur. Portal pressure increases and perfusion of the liver *via* portal vein is decreased. The combined effect of these changes in hepatic circulation on liver parenchyma is hypoxic damage of hepatocytes. Non-inflammatory centrilobular cell necrosis is found in nearly 70% of cases[20]. Reperfusion injury may contribute to hepatocyte damage[21]. Hepatocyte necrosis coordinates with release of free oxygen radicals and inflammation. Massive hepatocellular damage with a fulminant course is rare. Usually, portal hypertension and ascites are seen in chronic form. Both the acute and chronic forms result in severe centrilobular congestion and hepatocellular necrosis and atrophy. Within a few weeks after obstruction, fibrosis develops predominantly in the centrilobular area[21]. Within a few months, nodular regeneration may be seen predominantly in the periportal area. Progressive fibrosis, nodular regenerative hyperplasia and cirrhosis develop during the course of disease[22]. Interventional portosystemic shunts or development of portal venous collateral system may improve liver functions and delay the cirrhotic process[23].

The caudate lobe, which has direct venous drainage into the IVC, often undergoes compensatory hypertrophy. Caudate lobe hypertrophy is found in half of the cases and causes IVC stenosis. Obstruction of the portal vein is present in 10%-20% of cases and may be related to stagnant blood flow and underlying thrombophilic disorder[24].

DIAGNOSIS

BCS should be suspected in patients with: (1) Abrupt onset of ascites and painful hepatomegaly; (2) Massive ascites with relatively preserved liver functions; (3) Sinusoidal dilation in liver biopsy without heart disease; (4) Fulminant hepatic failure associated with hepatomegaly and ascites; (5) Unexplained chronic liver disease; (6) Liver disease with thrombogenic disorder.

Serum transferase levels may be more than five times the upper limit of the normal range, especially in the fulminant and acute forms of BCS. Serum alkaline phosphatase and bilirubin levels also increase. Serum albumin level decreases moderately.

Doppler ultrasonography of the liver, with a sensitivity and specificity of 85% or more, is the technique of choice for initial investigation when BCS is suspected[25]. Imagings of hepatic veins without flow signal, and with spider-web appearance, collateral hepatic venous circulation and stagnant, reversed or turbulent flow are indicative of BCS. Unvisualized or tortuous hepatic veins are common but non-specific sonographic findings of BCS, as they may be observed in advanced cirrhosis caused by other etiologies. Intrahepatic or subcapsular venous collaterals are sensitive sonographic findings of the disease, present in up to 80% of cases.

Magnetic resonance imaging (MRI) should be performed as a second-line imaging modality. MRI can show the hepatic vein thrombosis and evaluate the IVC, but it is more expensive than computed tomographic (CT) scanning. Three-dimensional contrast enhanced MR angiography has similar sensitivity to hepatic venography[26]. MRI is not as effective as sonography in demonstrating the intrahepatic collateral vessels and cannot show flow direction. CT scanning may be recommended for imaging the vascular anatomy and the configuration of the liver when a transjugular intrahepatic portosystemic shunt is considered. Unvisualized hepatic veins are suggestive of disease on CT, but false-positive or indeterminable results can occur in 50% of cases[27]. Contrast nephropathy from iodinated agents may occur.

Hepatic venography is the reference procedure for the evaluation of hepatic veins, extent of thrombosis and caval pressures. Inferior cavography should be performed to demonstrate stenosis or occlusion of the IVC. It should be considered when percutaneous or surgical shunts are planned. The disadvantages of hepatic venography are difficulty in cannulation of hepatic veins and requirement for a considerable amount of iodine-containing contrast agents. The diagnosis of BCS is confirmed by a spider-web pattern on hepatic venography.

Liver biopsy shows congestion, liver cell loss and fibrosis predominantly located in the centrilobular area. The congestion can be seen in heart failure and constrictive pericarditis. Perivenular fibrosis may be also found in diabetic or alcoholic patients. Liver biopsy is important in differentiation of BCS from veno-occlusive disease, which is characterized by nonthrombotic obstruction of hepatic venules by subendothelial swelling due to injury of sinusoidal wall. Veno-occlusive disease occurs following administration of toxic agents and is associated with bone marrow transplantation[28]. Since obstruction of small hepatic veins without the involvement of large ones is included in the definition of BCS, liver biopsy is required for differentiation from veno-occlusive disease.

BCS and cardiac disorders may have similar clinical features. In patients with suspected cardiac disorders like tricuspid regurgitation and constrictive pericarditis, differential diagnosis from cardiac disorders must be done. Echocardiography is helpful for differentiation, but further investigations are sometimes needed.

After the documentation of BCS, etiologic factors must be assessed. Hemogram, evaluation of peripheral blood, determination of coagulation factors and inhibitors, genetic tests for factor V and prothrombin, determination of antiphospholipid antibody and lupus anticoagulant, and flow cytometry for paroxysmal nocturnal hemoglobinuria should be performed. Bone marrow biopsy is helpful for diagnosis of primary myeloproliferative disorder and determination of total red cell mass. If available, peripheral blood or bone marrow cultures could be performed for assessment of spontaneous erythroid colony formation, a supportive finding of myeloproliferative disorder[29].

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