

BUDD-CHIARI SYNDROME

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ABSTRACT

Budd-Chiari syndrome (BCS) is a rare disease characterized by obstruction of the hepatic veins, regardless of mechanism and degree, in the absence of heart disease, pericardial disease or sinusoidal obstructive syndrome. In relation to etiology, BCS is classified in primary BCS, when it is caused by an intravascular thrombosis, and secondary BCS, when the obstruction is due to extrinsic compression or tumor invasion. The positive diagnosis is based on patient's medical history, clinical examination, and paraclinical investigations. The clinical picture is polymorphous. The most common signs and symptoms include fever, abdominal pain and abdominal tenderness on palpation, hepatomegaly, ascites, edema of the lower limbs, gastrointestinal bleeding and hepatic encephalopathy. Laboratory tests can detect the degree of liver injury, with decreased serum albumin, altered coagulation, hepatic cytolysis and cholestasis, while imaging investigations may reveal the

RÉSUMÉ

Le syndrome de Budd-Chiari

Le syndrome de Budd-Chiari (BCS) est une maladie rare caractérisée par une obstruction des veines hépatiques, quels que soient leur mécanisme et leur degré, en l'absence de maladie cardiaque, de maladie péri-cardique ou de syndrome obstructif sinusoidal. En ce qui concerne l'étiologie, le BCS est classé dans le BCS primaire, lorsqu'il est provoqué par une thrombose intravasculaire, et le BCS secondaire, lorsque l'obstruction est due à une compression extrinsèque ou à une invasion tumorale. Le diagnostic positif repose sur les antécédents médicaux du patient, son examen clinique et ses investigations paracliniques. Le tableau clinique est polymorphe. La fièvre, les douleurs abdominales et la sensibilité abdominale à la palpation, l'hépatomégalie, l'ascite, l'œdème des membres inférieurs, les saignements gastro-intestinaux et l'encéphalopathie

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venous obstruction. Regarding treatment, all patients with BCS are recommended systemic anticoagulation to reduce the risk of thrombus extension and prevention of further thrombotic episodes. Depending on patient's individual characteristics, angiography with or without stent, thrombolysis, trans-jugular intrahepatic portosystemic shunt and liver transplant are to be considered. The syndrome's severity and prognosis are dictated by the underlying disease, ranging from a possible curability to quick death.

Keywords: Budd-Chiari syndrome, hepatic vein obstruction, anticoagulants, trans-jugular intrahepatic portosystemic shunt.

INTRODUCTION

Budd-Chiari syndrome (BCS) is a congestive liver disease secondary to hepatic veins obstruction, due to either a thrombotic or a non-thrombotic event. The prognosis of patients with BCS ranges from a potential curability to death, as this syndrome may occur during the development of a severe hematological disease or during malignancies^{1,2}. The name of this syndrome comes from the English internist, George Budd, who in 1845 described the first three cases of venous hepatic thrombosis secondary to liver phlebitis induced by abscesses, and Austrian pathologist Hans Chiari, credited with the first pathological description of a liver with hepatic-vein-obstructive endo-phlebitis (1899).

EPIDEMIOLOGY

Budd-Chiari syndrome is a rare condition, its prevalence being estimated at about 1 case per 100.000 inhabitants, with geographical variations^{3,4}. Thus, in some Asian countries, such as Nepal, BCS is considered a relatively common cause of liver disease, while in Western countries it is a rare disease, with an incidence not exceeding 1 case in 2.5 million individuals per year⁴. BCS affects all races and the male-to-female ratio is approximately equal³. Related to geographical region, in Western countries hepatic vein obstruction is more common, unlike non-Western countries, where inferior vena cava obstruction is encountered more frequently. In regions such as

hépatique sont les signes et les symptômes les plus courants. Les tests de laboratoire peuvent détecter le degré de lésion hépatique, avec une diminution de la sérum-albumine, une modification de la coagulation, une cytolysé hépatique et une cholestase, tandis que des examens d'imagerie peuvent révéler une obstruction veineuse. En ce qui concerne le traitement, l'anticoagulation systémique est recommandée à tous les patients atteints de BCS afin de réduire le risque d'extension du thrombus et de prévenir d'autres épisodes thrombotiques. Selon les caractéristiques du patient, une angiographie avec ou sans endoprothèse vasculaire, une thrombolyse, un shunt portosystémique intrahépatique transjugulaire et une greffe du foie doivent être envisagés. La gravité et le pronostic du syndrome sont dictés par la maladie sous-jacente, allant d'une curabilité possible à une mort rapide.

Mots-clés: syndrome de Budd-Chiari, obstruction veineuse hépatique, anticoagulants, shunt portosystémique intrahépatique transjugulaire.

South Africa, India, Japan, Nepal and China, Budd Chiari syndrome is often caused by a membranous obstruction, while in the Western countries it is most commonly caused by thrombosis². The initial theory claimed a congenital cause for the membrane, but currently there are opinions saying that this is a consequence of thrombosis organization⁵. One possible trigger factor might be an infectious event. The symptoms of hepatic vein obstruction are similar to those of the liver segment of the inferior vena cava liver obstruction².

ETIOLOGY

Depending on the origin of the obstructive lesion, Budd-Chiari syndrome can be primary or secondary. Thus, if the obstruction is the result of a lesion such as endoluminal thrombosis, BCS is considered primary, while if the causes are either an extrinsic compression or invasion, it is secondary BCS¹. Risk factors for the development of primary and secondary BCS, respectively, are shown in Table 1².

Intravascular thrombosis is a major cause of hepatic venous obstruction. To initiate the pathological process, the interaction between one or more prothrombotic disorders and a trigger factor is necessary. At least one prothrombotic risk factor has been identified in 87% of patients with BCS⁶ and up to 46% of the patients had multiple risk factors⁶. Myeloproliferative neoplasms (MPN) are the main culprit². Of these, closely associated with hepatic vein thrombosis is polycythemia vera, while essential

Table 1. Risk factors for Budd-Chiari syndrome (adapted after Podolsky DK, Kalloo AN, Camilleri M, Shanahan F, Fitz JG, Wang TC, Yamada's Textbook of Gastroenterology Sixth edition, 2016: 2172–2175).

Primary Budd-Chiari syndrome	Secondary Budd-Chiari syndrome
<p>Acquired prothrombotic diseases:</p> <ul style="list-style-type: none"> • Myeloproliferative neoplasms (28%–49%) • Antiphospholipid antibodies (5%–25%) paroxysmal • Paroxysmal nocturnal hemoglobinuria (PNH) (9%–19%) • Behçet's disease (0%–33%)* • Hyperhomocysteinemia (37%) <p>Inherited prothrombotic diseases:</p> <ul style="list-style-type: none"> • Factor V Leiden mutation (7%–32%) • Protein C deficiency (4%–30%) • Protein S deficiency (3%–20%) • Antithrombin deficiency (3%–23%) • Prothrombin G20210A mutation (3%–12%) • Methylene-tetrahydrofolate reductase gene mutations (MTHFR mutations) (12%–22%) <p>Other causes:</p> <ul style="list-style-type: none"> • Oral contraceptives (6%–60%) • Pregnancy, puerperium (6%–12%) • Hypereosinophilic syndrome • Granulomatis venulitis • Ulcerative colitis 	<ul style="list-style-type: none"> • Hepatocellular carcinoma • Renal cell carcinoma • Adrenal carcinoma • Primary hepatic hemangiosarcoma • Epithelioid hemangioendothelioma • Sarcoma of the inferior vena cava • Right atrial myxoma • Hydatid cysts • Amebic or pyogenic abscess • Sarcoidosis • Trauma • Aspergillosis • Abdominal surgery

thrombocytopenia and idiopathic myelofibrosis are less frequent causes⁷. Hyperhomocysteinemia and methylene-tetrahydrofolate reductase gene mutations (MTHFR) are less important risk factors for splanchnic thrombosis⁸. Another risk factor for BCS is antiphospholipid antibodies syndrome, which can be associated with various connective tissue diseases. Consumption of oral contraceptives, pregnancy and confinement are risk factors for BCS, but most often they coexist with other risk factors^{2,9}. Although Behçet's disease can cause hepatic vein thrombosis, it is more likely to cause inferior vena cava obstruction². Inherited prothrombotic diseases (Table 1) have been described as risk factors for both BCS and portal vein thrombosis¹⁰. The major causes of secondary BCS are cancers and infections (Table 1). Uncommon causes are trauma, with the formation of intrahepatic hematomas, and granulomas caused by aspergillosis and sarcoidosis, that invade the hepatic veins.

PATHOLOGICAL COURSE

Obstruction of two or more major hepatic veins increases the sinusoidal pressure and reduces sinus blood flow. An obstruction in only one hepatic vein is generally clinically evident. The result of these hemodynamic changes is sinusoidal dilation and fluid filtering to the interstitial level. The filtrated fluid passes through the hepatic capsule when lymphatic drainage capacity is exceeded. This process leads to hepatic congestion, upper abdominal pain and ascites. Portal pressure increases and hepatic

perfusion decreases. The combined effect of these changes in the circulation is hypoxic injury of the hepatocytes, non-inflammatory centrilobular cell necrosis being found in about 70% of the cases¹. Reperfusion-induced injury might also contribute to hepatocyte damage. Hepatocyte necrosis is associated with the release of free radicals and secondary inflammation. A fulminant evolution of these pathologic processes is generally rare, as it is chronic. Both acute and chronic forms result in massive centrilobular congestion, necrosis and atrophy. A few weeks after obstruction, fibrosis appears, mostly in the centrilobular area, and after a few months, nodular regeneration can be observed in the peri-portal area. The disease is characterized by progressive fibrosis, cirrhosis and nodular regenerative hyperplasia¹.

POSITIVE DIAGNOSIS

Positive diagnosis is based on corroborating information obtained from the patient's medical history and clinical examination with the laboratory investigations. The most common signs and symptoms found in patients with BCS include fever, abdominal pain and abdominal tenderness on palpation, hepatomegaly, ascites, edema of the lower limbs, gastrointestinal bleeding and hepatic encephalopathy¹¹. The classical triad consists of abdominal pain, hepatomegaly and ascites. Abdominal pain is present in 61% of patients, hepatomegaly in 83% and ascites in 67%^{12,13}. BCS presentation may be acute, sub-acute or chronic, the last two being the most common. The severity

of symptoms depends on the extent of the lesion in the hepatic veins, the time passed after the appearance of the obstruction and the duration of the disease remaining untreated. A slower development in the obstruction leads to the formation of collateral vessels, which improves the sinusoidal congestion. Patients with acute presentation are more prone to have a fulminant evolution, with liver failure, coagulopathy, encephalopathy, and hepato-renal syndrome. However, in a chronic evolution with well-developed collateral vessels or the involvement of a single hepatic vein, the patient may have preserved liver function. Patients with obstruction of the inferior vena cava may present a sub-cutaneous venous network on the abdomen, anterior thorax and back, which represents the so-called collateral circulation. Portal vein thrombosis is present in approximately 15% of patients with BCS^{2,14}. These patients have a high prevalence of multiple risk factors and a reserved prognosis compared to patients with isolated BCS. Also, up to 20% of patients may be asymptomatic². For a positive diagnosis, both laboratory investigations and imaging investigations are necessary. Thus, serum aminotransferases and alkaline phosphatase may be normal or elevated². In acute forms, the aminotransferases levels exceed 5 times the normal value¹. Prothrombin and bilirubin values may also be normal or increased, although the presence of jaundice in BCS is not very frequent. The levels of albumin can be moderately decreased and the serum-ascites albumin ratio is greater than 1.1 g/dL². The low levels of protein C, protein S or antithrombin can be misleading, because they can be the mark of both a coagulopathy and of chronic liver disease development in the evolution of BCS².

In almost all cases, the diagnosis of BCS can be determined by non-invasive imaging methods, such as Doppler ultrasound, CT, or MRI-angiography. Current guidelines recommend performing either a CT scan or an MRI to confirm the diagnosis only if the ultrasound is not available¹⁵. Imaging evaluation may reveal obstruction or lack of blood flow in a major liver vein or in the intrahepatic portion of the inferior vena cava, the formation of collateral vascular networks, a nodular aspect of the hepatic parenchyma, increased size of the caudate lobe, ascites and splenomegaly². If the hepatic veins are perceived as normal, with usual blood flow, the diagnosis of BCS is excluded. Ultrasound is superior to MRI in detecting the intrahepatic collateral vascular networks². Liver biopsy is of limited value, due to the variability of injuries¹⁶. However, biopsy is the only method that can establish the diagnosis of BCS when lesions are located in the small intrahepatic veins¹⁶. Currently, the development of radiological diagnostic means resulted in limiting the use of invasive methods, such

as venography or liver biopsy, in patients in whom the diagnosis remains uncertain or in order to characterize the anatomy prior to treatment¹⁶⁻¹⁸.

The presence of liver regeneration nodules is common in patients with BCS. Since these patients are also exposed to a greater risk of developing hepatocellular carcinoma, it is very important to differentiate between benign and malignant nodules¹⁶⁻¹⁹.

BCS patients may have similar features to those with heart disease and tricuspid regurgitation or constrictive pericarditis^{20,21}. Thus, if the presence of cardiac disorders is suspected, it is necessary to make a differential diagnosis, most commonly using echocardiography^{1,22}.

In addition to the positive diagnosis of BCS, it is necessary to identify the predisposing factors. In about half of the cases, multiple factors are present. Thus, it is recommended that a complete epidemiological study be performed, even after the first identification of a risk factor².

TREATMENT OF BUDD-CHIARI SYNDROME

The management of patients with BCS involves the following steps:

1. Anticoagulant treatment of the prothrombotic conditions that led to BCS, prevention or treatment of complications of portal hypertension.
2. Angioplasty, with or without stent.
3. Trans-jugular intrahepatic portosystemic shunt (TIPS), if angioplasty is not available or has not been effective^{23,24}.
4. Evaluation for liver transplant if TIPS proved inefficient^{2,10}.

Anticoagulant therapy is recommended to all patients with BCS, even to those that do not have a prothrombotic factor or who are asymptomatic, in the absence of possible adverse reactions. The anticoagulation objective is to reduce the risk of thrombus extension and prevent new thrombotic episodes^{2,25}.

The data on the benefits of thrombolysis in patients with BCS are insufficient. Current studies suggest that the best results are obtained by local injection of the thrombolytic agent, rather than systemic thrombolysis, in the case of incomplete and recent thrombosis²⁶.

Angioplasty, with or without stent, should be considered in patients with a short stenosis. Better results are obtained if anticoagulant therapy is continued for at least 6 months²⁷.

The use of TIPS in patients with BCS has recently seen an increase. Current guidelines recommend consideration of TIPS in patients who did not show a significant improvement on anticoagulant treatment. Morbidity and mortality are lower in the case of TIPS

than in surgical shunts. On the other hand, the hemorrhagic complications of TIPS are more common in patients with BCS than other chronic liver diseases, but the incidence of encephalopathy can be less²⁸. Liver transplant is the elective treatment in patients with acute BCS and fulminant hepatic failure and in patients that get to the final stage after a chronic evolution^{29,30}. Recent data suggest that liver transplant increases 1-year survival rates up to 75% and up to 65% in 5 years³¹.

BCS prognosis varies depending on the underlying condition. The treatment is aimed at slowing disease progression and improving patients' quality of life. Being subjected to a higher risk of infection, it is important that these patients should be advised regarding personal hygiene and influenza or pneumococcal vaccination. Also, taking into consideration the psychological impact of this disease, it is necessary to provide a support system³.

CONCLUSIONS

BCS is a rare disease with a severe prognosis, if not properly diagnosed and treated. The identification of risk factors is helpful for the diagnosis. Modern treatments, including the interventional ones, may improve the prognosis of patients with BCS, depending on the etiology of the disease.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

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