Vascular liver disorders (I): diagnosis, treatment and prognosis of Budd-Chiari syndrome

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ABSTRACT

Budd-Chiari syndrome (BCS) is a venous outflow obstruction of the liver that has a dismal outcome if left untreated. Most cases of BCS in the Western world are caused by thrombosis of the hepatic veins, sometimes in combination with thrombosis of the inferior vena cava. Typical presentation consists of abdominal pain, hepatomegaly and ascites, although symptoms may vary significantly. Currently, a prothrombotic risk factor, either inherited or acquired, can be identified in the majority of patients. Moreover, in many patients with BCS a combination of risk factors is present. Myeloproliferative disorders are the most frequent underlying cause, occurring in approximately half of the patients. Recent discovery of the Janus Kinase 2 (JAK2) mutation has significantly contributed to the diagnosis of myeloproliferative disorders. Anticoagulation is indicated for all patients with BCS and additional therapy depends on the severity of symptoms and the extent of venous obstruction. A stepwise therapeutic approach is recommended, with increasing invasiveness and guided by the response to previous treatment. A transjugular intrahepatic portosystemic shunt (TIPS) is proving to be a good therapeutic option in patients with BCS, diminishing the need for surgical shunts. When all other therapy is unsuccessful or in patients with fulminant hepatic failure, a liver transplantation should be considered. Advances in diagnosis and treatment have dramatically improved the prognosis of patients with BCS. Still, many aspects of this complicated disorder remain to be clarified.

KEYWORDS

Anticoagulation, Budd-Chiari syndrome (BCS), hepatic vein thrombosis, myeloproliferative disorder (MPD), transjugular intrahepatic portosystemic shunt (TIPS)

INTRODUCTION

Thrombosis involving the liver vasculature is rare but constitutes a potentially life-threatening situation. Budd-Chiari syndrome (BCS) is characterised by thrombosis of the hepatic outflow tract. It is defined as a venous obstruction that can be located from the level of the small hepatic veins up to the junction of the inferior vena cava with the right atrium (figure 1).1 Hepatic outflow obstruction related to right-sided cardiac failure or sinusoidal obstruction syndrome (SOS, also known as veno-occlusive disease)2 is not included in the definition of BCS. The clinical symptoms of BCS were first described by Budd in 1845,1 followed by Chiari’s report of the underlying histopathology half a century later.4 Over the past years, improved imaging techniques and new insights into

Figure 1. Schematic overview of the vasculature of the liver

In Budd-Chiari syndrome venous outflow from the liver is blocked, this obstruction can range from the small hepatic veins up to the inferior vena cava.
Potential causative factors have significantly contributed to the diagnosis and treatment of BCS. Nevertheless, due to the rarity of this disorder, most existing knowledge is based on data from (small) retrospective series. In this review we will give an overview of the current diagnosis, treatment and prognosis of BCS.

**Clinical Manifestations of Hepatic Venous Obstruction**

Obstruction of the hepatic veins gives rise to several haemodynamic changes, such as a decreased sinusoidal blood flow and an increased sinusoidal blood pressure, which can eventually lead to portal hypertension. Venous congestion also provokes ischaemia and subsequent necrosis of sinusoidal hepatocytes (figure 2). Significant hypoxic damage can result in a deterioration of hepatic synthetic function. Over time, hepatocytes are replaced by fibrosis, predominantly localised in the centrilobular area. Nodular regeneration is also regularly seen in patients with BCS and ultimately, cirrhosis may develop. Other potential consequences of hepatic venous obstruction are portal vein thrombosis and hypertrophy of the caudate lobe. In approximately 15 to 20% of cases of BCS concomitant portal vein thrombosis is identified. Because the caudate lobe is the only liver segment with direct venous drainage into the inferior vena cava, compensatory hypertrophy often occurs. Caudate hypertrophy itself can subsequently cause compression and stenosis of the inferior vena cava, further contributing to the already existent venous congestion.

Clinical presentation of patients with BCS is heterogeneous and ranges from the absence of symptoms to severe liver failure. The classical triad consists of abdominal pain, ascites and hepatomegaly but other possible symptoms are nausea, fever and jaundice. The severity of disease is influenced by the extent of thrombosis, the rapidity of onset and the ensuing effect of compensatory mechanisms such as the formation of collateral veins. In the past years, different classifications (i.e. acute, subacute and chronic) have been used to describe patients with BCS according to the duration and severity of symptoms. However, the prognostic value of these descriptive categories has not been validated. Instead, more recent studies have attempted to determine distinct prognostic classes based on the outcome of clinical and laboratory assessments.

Despite the major haemodynamic changes involving the liver, synthetic function is often relatively spared. However, this does not preclude a late decline in general condition and liver function. During the course of the disease, portal hypertension frequently develops and may be complicated by bleeding from gastro-oesophageal varices. In a significant number of patients signs of portal hypertension, such as splenomegaly or oesophageal varices, are already present at diagnosis, implicating that an acute thrombotic event can be superimposed on a long-standing obstruction. Less common, an episode of gastrointestinal bleeding is the first presenting sign of BCS. In contrast, ascites is an important complication of hepatic venous obstruction and a frequent cause of morbidity. Control of ascites is therefore important in the management of patients with BCS.

**Aetiology**

BCS can be further classified as primary or secondary, depending on the underlying cause and the type of venous obstruction. If an endoluminal venous lesion is present, such as thrombosis or an inferior vena cava web, BCS is considered primary. The secondary form consists of venous obstruction caused by external invasion or compression of the venous lumen, as is the case with malignant tumours or large cysts. In Western countries, thrombosis is the most frequent cause of venous obstruction in...
BCS. Whereas in the past many cases were designated as idiopathic, it has nowadays been established that in most patients with BCS an underlying risk factor predisposing to thrombosis is present. Both inherited (e.g. Factor V Leiden mutation, deficiencies in protein C, protein S and antithrombin) and acquired (e.g. paroxysmal nocturnal haemoglobinuria, antiphospholipid syndrome) procoagulant disorders have been associated with BCS, of which myeloproliferative disorders are the most common (table 1). When both overt and latent forms are taken into account, approximately 50% of patients with BCS are shown to have an underlying myeloproliferative disorder (MPD). Moreover, it has become clear that in a large proportion of patients more than one risk factor can be identified. In studies of BCS patients with a proven MPD, additional prothrombotic factors were found in more than 30% of the cases.

A common finding in these patients is a patchy distribution of congestion and haemorrhage throughout the liver parenchyma.

**Table 1. Risk factors for Budd-Chiari syndrome**

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Acquired</th>
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<tbody>
<tr>
<td>Factor V Leiden mutation</td>
<td>Myeloproliferative disorder</td>
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<tr>
<td>Prothrombin (factor II) mutation</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>Protein S deficiency</td>
<td>Behçet’s disease</td>
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<td>Antithrombin deficiency</td>
<td>Oral contraceptives</td>
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<td></td>
<td>Pregnancy and puerperium</td>
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<td></td>
<td>Hyperhomocysteinaemia</td>
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</table>

**Diagnostic Work-up**

Presence of hepatic venous outflow obstruction should be suspected in patients with (acute onset of) ascites and painful hepatomegaly or when refractory ascites is present, typically in combination with relatively normal liver function tests. BCS should also be considered if liver disease is observed in patients with known thrombophilia. Physical examination and laboratory investigations are usually not very specific. In most cases diagnosis can be accurately assessed with noninvasive radiological imaging. Doppler ultrasonography is the initial technique of choice and has high sensitivity and specificity. Findings that support the diagnosis of BCS are absence of flow or retrograde flow in the hepatic veins and the presence of thrombosis within the hepatic veins or inferior vena cava. Other indicative features are intrahepatic or subcapsular collateral veins and failure to visualise the hepatic veins. Computerised tomography (CT) and magnetic resonance imaging (MRI) are also frequently applied to demonstrate occlusion of the hepatic veins, inferior vena cava or both. With these techniques the liver parenchyma itself is usually better visualised to show perfusion details or necrotic areas (figure 3). Secondary causes of BCS, such as tumoural invasion or cysts causing venous compression, can also be identified with these different imaging modalities. Invasive hepatic venography is still regarded as the reference procedure but is nowadays only performed if venous pressure measurements are required.

A liver biopsy is not required to confirm the diagnosis of BCS but can be carried out to rule out other causes. Due to the high risk of sampling error, a biopsy is insufficient to study the severity of BCS. Typical histological findings of hepatic venous outflow obstruction are congestion, loss of hepatocytes and fibrosis, most often in the centrilobular area. Histological abnormalities usually show an inhomogeneous distribution depending on the involved venous obstruction (figure 4). Other parenchymal changes that can be found in approximately 25% of patients along the course of the disease are regenerative nodules. These benign nodules are thought to develop as a result of an imbalance between arterial and portal blood flow. Usually, multiple regenerative lesions are present that can range in diameter from a few millimetres up to 7 cm. Although malignant hepatic lesions are rarely seen in patients with BCS, it may be difficult to distinguish regenerative macronodules from hepatocellular carcinoma.

An equally important part of the diagnostic work-up in patients with thrombosis of the hepatic veins is the...
identification of underlying thrombophilic factors. As mentioned previously, in a significant number of patients multiple aetiological factors can be identified. Therefore, the presence of one thrombophilic factor should not preclude further investigations of other possible risk factors. Diagnosis of an MPD can prove to be difficult in patients with BCS because in many cases typical changes in peripheral blood (i.e. high levels of haemoglobin or platelets) are absent and conventional diagnostic criteria are often not met. In the past, these so-called occult or latent forms could only be detected by bone marrow biopsy or the existence of endogenous erythroid colony formation. Recently however, the diagnosis of (occult) MPDs has been facilitated by the discovery of the Janus Kinase 2 (JAK2) mutation. This acquired gain-of-function mutation of the JAK2 tyrosine kinase can be demonstrated in the majority of patients with an MPD. Furthermore, several studies have already pointed out that the JAK2 mutation is proving to be a reliable screening marker for MPDs in patients with BCS. Because not all cases of MPD are JAK2 positive and further characterisation is often needed, a bone marrow biopsy will still be required in most patients.

TREATMENT

Due to the rarity of the disorder, no controlled studies have been performed in patients with BCS. Therefore, most current knowledge and recommendations are based on case reports, retrospective studies and expert opinions. Furthermore, because experience with the treatment of this vascular liver disorder is often limited, all patients diagnosed with BCS should preferentially be referred to a specialised liver centre. The first step in the treatment of patients with BCS is initiation of anticoagulant therapy to prevent extension of the thrombosis. Although evidence remains circumstantial, lifelong anticoagulation is recommended in all patients with this life-threatening form of thrombosis, providing that there are no contraindications. Underlying thrombophilic conditions should be identified and treated where possible. The next step in the management process concerns the manifestations and complications of liver disease. In the past, invasive treatment for patients with BCS was frequently applied and many patients were treated with surgical portosystemic shunts or liver transplantation. Recently, however, a more stepwise approach has been advocated where therapeutic procedures are performed in order of increasing invasiveness and based on the response to previous treatment (figure 5). This is supported by the finding that some patients can be adequately treated in a noninvasive manner. Nevertheless, if ascites and other complications cannot be controlled with anticoagulation and diuretics alone, further (invasive) treatment steps are required. Percutaneous transluminal angioplasty (PTA) has

![Liver biopsy specimen (haematoxylin and eosin (HE) staining, x100)](image)

Top panel: depicting areas of haemorrhage (H) and congestion surrounding the central veins (zone 3). The periportal area (zone 1) around the portal vein (PV) branches is relatively spared. Bottom panel: further enlarged view of liver parenchyma (HE staining, x200) depicting a central vein (CV) of a liver lobulus surrounded by an area of fibrosis (F). This so-called pericentral fibrosis is a typical finding in patients with Budd-Chiari syndrome (BCS).

**Figure 4.** Liver biopsy specimen (haematoxylin and eosin (HE) staining, x100)

**Figure 5.** Treatment algorithm for patients with Budd-Chiari syndrome

<table>
<thead>
<tr>
<th>Step</th>
<th>Procedure</th>
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<tbody>
<tr>
<td>1</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>2</td>
<td>Recanalization procedure (PTA with stenting* or thrombolysis)</td>
</tr>
<tr>
<td>3</td>
<td>TIPS (or surgical shunt)</td>
</tr>
<tr>
<td>4</td>
<td>Liver transplantation</td>
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</table>

*Only possible in case of short-length stenosis. PTA = percutaneous transluminal angioplasty; TIPS = transjugular intrahepatic portosystemic shunt.
been successful in a number of patients but should only be performed if a short-length stenosis is present.44-45 Systemic or local thrombolytic therapy has also been attempted as a recanalisation procedure, with variable success. Recent evidence suggests that it should be executed with great caution due to the high risk of bleeding complications (unpublished data). When these recanalisation techniques are not eligible or unsuccessful at controlling symptoms of ascites and portal hypertension, a shunting procedure is indicated. Surgical portosystemic shunting has now been almost completely abandoned as a treatment modality for patients with BCS. In a recent study it was performed in less than 2% of the patients.19 Moreover, other studies have not been able to demonstrate a survival benefit for patients treated with surgical shunts.18,13 This could be explained by a high perioperative mortality and a risk of shunt dysfunction or thrombosis.44,45 Instead, more patients are currently being treated with a transjugular intrahepatic portosystemic shunt (TIPS) to lower portal venous pressure and decompress the sinusoids. Over the past years it has become increasingly clear that the outcome of TIPS in patients with BCS is good. The procedure is less invasive than surgical shunting, it can be successfully performed in most patients and there are fewer complications.46-47 Furthermore, in high-risk patients, TIPS placement may even improve survival.48 Nevertheless, when shunting procedures do fail and clinical deterioration occurs, orthotopic liver transplantation (OLT) is the last treatment option for patients with BCS. Patients presenting with fulminant liver failure should also be considered for liver transplantation. Survival rates and graft function after OLT in patients with BCS are comparable to patients transplanted for other causes.49,50 Additionally, patients without an underlying MPD.21,22 Also, survival does not seem to be impaired by the recent shift in management leading to a less invasive treatment approach.19,41 In contrast, the presence of concurrent portal vein thrombosis has been associated with a poor prognosis in patients with BCS.6,7 Further studies are warranted to investigate the effect of different prothrombotic factors on prognosis and to identify specific patients that require early invasive treatment.

**REFERENCES**


Hoekstra, et al. Diagnosis, treatment and prognosis of Budd-Chiari syndrome.


