Diagnosis and therapy of Budd Chiari syndrome

Iulianna Lupasco, Vlada-Tatiana Dumbrava

Research Laboratory of Gastroenetrology, "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Abstract

Budd-Chiari syndrome is described as a disorder characterized by the obstruction of hepatic venous outflow. The first description of the syndrome was done by George Budd in 1846. The etiology of the disease is multifactorial and requires differential diagnosing. The prognostic evaluation of patients with liver outflow obstruction differentiates special groups for further treatment procedures. The stepwise approach of Budd-Chiari syndrome allows the finding of the right technique on an individual basis for every patient.

Keywords: Budd-Chiari syndrome, rare disease, prognostic evaluation, stepwise therapy

Budd-Chiari syndrome can be defined as an uncommon disorder characterized by the obstruction of the hepatic venous outflow. Despite belonging to a group of rare diseases, this disease requires careful attention, timely diagnosing, correct understanding of physiological changes in the patient's body and venous outflow correction in specialized centers.

The venous obstruction may be thrombotic or non-thrombotic anywhere along the venous course from the hepatic venules to the junction of the inferior vena cava (IVC) up to the right atrium [1]. Due to the pathophysiologic process the result is an interruption or diminution of the normal flow of blood out of the liver.

A clinical syndrome of hepatic veins occlusion was described for the first time by George Budd in 1846 [2]. Fifty-three years later (1899), Hans Chiari enriched the first description with clinical-pathological elements. Pathophysiological background of Budd–Chiari syndrome (BCS) was unknown and several authors proposed different hypotheses such as syphilitic disease, endophlebitis, and trauma. In 1912 Thompson and Turnbull claim that the initial event is the thrombosis; after this, in 1948 Blakemore performed the first surgical portosystemic shunt. Parker in 1959 revealed the importance of an underlying condition of thrombophilic changes through his work of literature review and found an association between BCS and some conditions such as polycythemia, pregnancy, estrogenic therapy, and published the first landmark manuscript. In the following years, the use of anticoagulants was proposed, but only in the mid-1980s, such therapy became generalized, with a consequent improvement of the BCS patients' survival. However, the initial fear of hemorrhagic complications discouraged this therapeutic approach, therefore different types of portosystemic shunts were conceived, but were associated with high morbidity and mortality. Main pylons of BCS treatment represented liver transplantation (1976) and trans-jugular intrahepatic portosystemic shunt (1993). Such progress moved the treatment of BCS to the modern concept of stepwise therapy.

The etiology of Budd-Chiari syndrome is multifactorial. However, most patients with BCS have underlying thrombotic changes with thrombosis, followed by hepatic vein obstruction although in approximately one third of patients, the condition is idiopathic. A venous obstruction can be of venous origin or an intra-/extrahepatic space-occupying lesion compressing/invading the venous outflow.

Causes of Budd-Chiari syndrome include the following (see Table I).

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Address for correspondence: flowercat_2004@yahoo.com

Table I. Etiology factors of BCS.

Hematologic disorders	Hepatic venous stenosis
Inherited or acquired thrombotic diathesis [3]	Hypoplasia of the suprahepatic veins
Pregnancy and postpartum [4]	Postsurgical obstruction
Oral contraceptives [3]	Posttraumatic obstruction
Chronic infections	Malnutrition [3]
Chronic inflammatory diseases	Total parenteral nutrition (TPN): Budd-Chiari syndrome has been reported as a complication of TPN via an IVC catheter in a neonate
Tumors	
Congenital membranous obstruction	

The origin of the obstructive lesion defines primary or secondary BCS. In case of obstruction as the result of endoluminal venous lesion-like thrombosis, it is considered primary BCS. In case of occlusion, originating from neighboring structures like extrinsic compression or tumor invasion it is considered secondary BCS [5].

Budd-Chiari syndrome incidence is reported in literature only in few studies, due to its rareness. According to the study by Rajani R. et al. an incidence of about 1 case per million population per year was found in Sweden [6], while Ollivier Hourmand and colleagues found BCS in 4.04 per million inhabitants in France (primary BCS was identified in myeloproliferative neoplasms (48%). At the same time use of oral contraceptives (35%), and factor V Leiden (16%) were found as the highest risk factors [7]. A retrospective (2009-2013) nation-wide, population-based study in South Korea found a total of 424 patients with Budd-Chiari syndrome, with an average age- and sex-adjusted prevalence of 5.29 per million population [8]. The female-to-male ratio was 1.8, the median age was 51 years, and the annual case-fatality rate was 2.8%.

Clinical presentation is deeply connected to the place and origin of the venous obstruction, having similar features with liver congestion followed by classic triad of symptoms: hepatomegaly, right upper quadrant pain, and ascites occurrence. These clinical outcomes can develop differently on a timeline. If the liver has time to develop collaterals and decompress, patients can be asymptomatic (≤20%) or present with few symptoms. As the syndrome progresses, liver injury becomes irreversible, once there is lobular collapse, it can lead to portal hypertension and liver failure with corresponding symptoms (for example, encephalopathy, hematemesis) [9].

Thus, from the degree and underlying conditions BCS can be defined in several forms:

- Fulminant form (rare - 7%, onset ≤ 2 months) with acute hepatic failure, along with ascites, tender hepatomegaly, jaundice, and renal failure; in laboratory findings 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 with increasing of serum alkaline phosphatase and bilirubin levels;
- Acute form (up to 6 months);
- Subacute form, as the most common (6 months - years), with main features of rapid development of abdominal pain, ascites, hepatomegaly, jaundice, and possible renal failure; in ascitic fluid high protein concentrations (>2 g/dL); the serum ascites–albumin gradient is usually less than 1.1;
- Chronic form (takes months to years) characteristic presentation with progressive ascites; jaundice is absent; approximately 50% of patients also have renal impairment; laboratory findings are not specific in case of ascites development decreasing in serum albumin levels.

The Budd-Chiari syndrome should be suspected in any symptomatic or asymptomatic patient with acute or chronic liver disease. According to recent guideline, imaging, as noninvasive procedure, is essential for the early identification and evaluation of the BCS. Doppler ultrasound is the first line of investigation for BCS due to its high sensitivity and specificity of more than 85%. Magnetic resonance imaging and computed tomography have to be used for diagnostic confirmation [5] in special cases.

Doppler sonography at the corresponding level can show high flow velocities with turbulence at the level of the stenosis and low flow velocity proximally in phase of breathing. Intrahepatic collaterals are of specific diagnostic criterion for BCS, and can extend from an occluded hepatic vein to a nonoccluded hepatic vein or even to the caudate lobe veins. Hepatomegaly, regenerative nodules are nonspecific features but also can be found.

Liver biopsy with further histology is not highly recommended being an invasive procedure and is used only in pretransplant settings and in case of other venocclusive diseases.

In the management of Budd-Chiari syndrome the main goal is restoring the venous flow no matter of the obstacle placement. In dependence of multiple etiological conditions of this disease, the stepwise approach was elaborated in leading patients from one possible technique to another in order to fulfill the key criteria of the treatment [5].

After the diagnosing of BCS there appears the question of forecasting the patient evolution and survival. The existing prognostic scores: Clichy prognostic index [PI], New Clichy PI, Rotterdam BCS index, and BCS-TIPS PI are based on some well-known parameters such as Child-Pugh score, age, serum creatinine, prothrombin, bilirubin and albumin (Table II).

Table II. Prognostic scores in BCS survival rate prediction.

Score	Formula	Cut off	Predicted survival rate
Clichy prognostic index [PI] [10]	(Ascites score 0.75)* + (Child-Pugh score 0.28) + (age 0.037) + (creatinine 0.0036)	5.4 (range from 3.4 to 9.1)	At 5 y. ≤5.4: 95% >5.4: 65%
New Clichy PI [11]	0.95 ascites score + 0.35 Child-Pugh score + 0.047 age + 0.0045 serum creatinine + 2.2 type III** - 2.6	5.1 (range from 2.0 to 9.7)	At 5 y. <5.1: 100% ≥5.1: 65%
Rotterdam BCS index [12]	1.27 encephalopathy + 1.04 ascites + 0.72 prothrombin time + 0.004 bilirubin	Class I: 0–1.1 Class II: 1.1–1.5 Class III: ≥1.5 (range from 0.02 to 4.03)	At 5 y Class I: 89% Class II: 74% Class III: 42%
TIPS-BCS PI [13]	Age (years) 0.08 + bilirubin (mg/dl) 0.16 + international normalized ratio (INR) 0.63	7	1-year OLT-free survival ≤7 95% >7 12%
BCS-intervention-free survival prognostic score [14]	Ascites [yes = 1, no = 0]*1.675 + ln creatinine [lmol/L]*0.613 + ln bilirubin [lmol/ L]*0.440)	Interval I: ≤5 Interval 2: 5–6 Interval 3: ≥6	Intervention-free Survival Interval I: 78.3% Interval 2: 27.8% Interval 3: 6.8%
BCSurvival score [14, 15]	Age/10*0.370 + ln creatinine [lmol/L]*0.809 + ln bilirubin [lmol/L]*0.496)	Interval I: ≤7 Interval 2: 7–8 Interval 3 ≥8	Probability survival Interval I: 87.5% Interval 2: 63.3% Interval 3: 42.9%

*Ascites score: 1- absent with free sodium intake and no diuretic agents; 2- easy to control with sodium restriction or diuretic agents; and 3, resistant to this treatment

**Type III: is a binary variable coded as 1- for patients with clinic-pathological findings of acute injury overlapped chronic lesions, and 0- for the other patients, BCS.

All these scores are useful in different groups of patients, as the BCS-specific prognostic score, for example, in predicting post liver transplantation survival [16]. Unfortunately, none of them specialized to monitor the follow up of individualized therapy approach.

The therapy starts from medication of thrombotic changes with anticoagulation remedies with monitoring of hematologic parameters, under control of other associated conditions. In case of ineffectiveness of this therapy, another step is recommended, such as angioplasty, stenting or thrombolysis. Each of them have both benefits and pitfalls, being used in less than 10% of patients with some positive results if were provided in early stages of disease development [17-20]. Experience of reversing the hepatic venous outflow obstruction with thrombolytic agents like streptokinase, urokinase, recombinant tissue-type plasminogen activator (rt-PA) is present only in a few studies and needs to be more investigated. Transjugular intrahepatic portosystemic shunt (TIPS) became a new modality in surgical approach in BCS with a lower morbidity and mortality rate comparing to abdominal surgery and is feasible in most patients with inferior vena cava obstruction (IVC) and in those with severe IVC stenosis [21]. As it can be seen, every approach of this stepwise management has its own place and individual patient. However, in case of liver failure the salvage therapy is liver transplantation, which is the last and only one possible resolving method for patient survival. Anticoagulation medication needs to be continued in most BCS patients after liver transplantation (LT). Screening patients with BCS for hepatocellular carcinoma is essential in follow up of BCS patients, especially after LT. Distinction between benign and malignant liver nodules is a difficult process and needs investigation at specialized medical centers. After endoscopic and surgical manipulations a close follow up is needed due to possible complications that can develop such as stent displacement and replacement, balloon dilation necessity, etc.). The anticoagulant therapy should be monitored by hematologic parameters, in the case of liver transplantation in lifelong basis.

Conclusions

1. Budd-Chiari syndrome is one of the rare diseases that has a multifactorial origin that should be diagnosed on time with thorough management.

2. The prognostic evaluation of patients with liver outflow obstruction differentiates special groupsfor further treatment procedures.

3. The stepwise approach of Budd-Chiari syndrome allows the finding of the right technique on an individual base for every patient.

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