A Review of Budd Chiari Syndrome

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Abstract

Budd - Chiari Syndrome (BCS) is a rare entity whose incidence is estimated at one in one hundred thousand. It consists of complete or partial obstruction of venous outflow at any location from the small hepatic veins to the hepatic portion of the inferior vena cava. It can be classified according to its etiology into primary BCS when there is venous obstruction and secondary disease when obstruction is attributed to extrinsic compression or invasion due to a lesion outside of the veins such as neoplasms or cysts. In most cases it presents as sudden onset of abdominal pain, ascites and hepatomegaly, but it may be asymptomatic. A definitive diagnosis is established by imaging, but basic laboratory tests and other studies must also be done. Diagnostic imaging techniques include Doppler ultrasonography, computed tomography, magnetic resonance imaging and digital subtraction angiography. The latter is considered to be the gold standard. The first therapeutic measure to be undertaken for these patients is anticoagulation with low molecular weight heparin followed by vitamin K antagonists. Most patients require a multidisciplinary approach and step by step treatment including radiological procedures, balloon enteroscopy, stenting, transjugular intrahepatic portosystemic shunt (TIPS), decompression surgery and finally, liver transplantation.

Keywords

Budd-Chiari syndrome, Doppler ultrasonography, CT scan, Digital Subtraction Angiography, Liver Transplant.

INTRODUCTION

Budd Chiari Syndrome (BCS) is a rare clinical entity which was first described in 1845 by Budd and later described by Chiari in 1899. The clinical manifestations of BCS appear as the result of partial or complete obstruction of venous outflow from small hepatic veins to the hepatic portion of the IVC (IVC). (1-4) In 2003 a panel of experts issues a consensus on the issue which excluded obstruction caused by heart disease, tumors or sinusoidal obstruction syndrome from this definition. The result is a definition of BSC as the result of obstruction of hepatic venous flow anywhere from the hepatic venules through to any part of the IVC until it arrives at the right atrium. (5)

This syndrome can be classified as primary or secondary, depending on the origin of the obstruction. It is considered primary if the obstruction is the result of an intraluminal venous injury such as thrombosis, and secondary when the obstruction is due to extrinsic compression of the venous system or to invasion by a tumor. (6, 7)

EPIDEMIOLOGY

The true incidence of BCS is unknown because thre have been very few studies of it. (8) Nevertheless, most authors ascribe an incidence of one case per one hundred thousand people in the general population of the world. (9) The incidence varies according to the place. In Nepal, it is the

leading cause of hospitalization due to liver disease while in Japan and Europe reports of patients with BCS are rare. (10, 11) The level of obstruction of hepatic venous flow and incidence by age and sex also vary according to location. In Asia, BCS is generally secondary to obstruction of the flow of the IVC or the flow between the IVC and hepatic veins, and most commonly occurs in male patients close to 45 years of age. In other countries, the obstruction is usually located in the hepatic veins, and and most commonly occurs in women with an average age of 35 years. (10)

ETIOLOGY

BCS can be divided into primary and secondary. It is primary when the cause of the obstruction is a venous disease such as thrombosis or phlebitis, and secondary when it is due to compression or invasion of an injury that originates outside of the veins such as tumors, abscesses, intrahepatic cysts and hematomas. (8). BCS has been shown by the literature to be associated with prothrombotic states. (12, 13, 14) A 2009 study by Darwish et. al. found that 84% of patients with BCS had at least one thrombophilic disorder and that 74% of these same patients had more than one prothrombotic condition of which most were myeloproliferative disorders. (38) It has even been reported that up 53% of patients with BCS have hidden or latent myeloproliferative disorders. (15,1 6) Janssen and colleagues concluded that mutation of Factor V Leiden and protein C deficiency are important risk factors for development of BCS. (17)

The use of combined oral contraceptives (COC) has also been associated with BCS and is documented in up to 33% of patients with this condition. (18) A case-control study published in 1986 by D. Valla et. al. showed that patients who had recently used COC had a 2.37 times higher risk of thrombosis of the hepatic veins than did patients who had not used these drugs. (19) It has been suggested that many patients who develop BCS related to COC use and patients who develop BCS during pregnancy may have some underlying thrombophilia. (20, 21) It has even been suggested that mutation of Factor V Leiden is associated with the use of COC. (22) It has been proposed that it is unlikely that isolated mutations of Factor V Leiden cause thrombosis in the absence of other congenital or acquired prothrombotic factors. A study of Deltenre and collaborators supports this thesis. In that study, 70% of patients with BCS had this mutation but also had one or more associated risk factors suggesting that this mutation alone is not sufficient to induce thrombogenisus. (23) Following from this, it has been suggested that patients with BCS or venous thromboembolic disorders and carriers of Factor V Leiden mutations be screened for other acquired and hereditary risk factors. (24) Polycythemia vera has also been found to be associated with BCS. (25, 26) another hematologic disorder that is classically associated with BCS is paroxysmal nocturnal hemoglobinuria, but to date too few studies have been done to support a strong relationship with this condition. (27, 28)

Other conditions including ulcerative colitis, celiac disease, liver tumors and Behçet's disease have been associated with BCS (Table 1). (29-32)

Table 1. Factors associated with BCS

Factors associated with BCS
Myeloproliferative neoplasms
JAK2
Factor V Leiden thrombophilia
Factor II Mutation
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Recent use of COC
Recent Pregnancy
Antiphospholipid syndrome
Hyperhomocysteinemia
Paroxysmal nocturnal hemoglobinuria
Behcet's disease
Celiac Disease
Ulcerative Colitis

PATHOGENESIS

The initial pathophysiological event in BCS is obstruction of venous flow between hepatic venules and the suprahepatic segment of the IVC. Blockage of a single hepatic vein is not sufficient for manifestation of the syndrome: at least two veins must be blocked for its clinical presentation. The consequence of this obstruction is a complex hemodynamic change with increased hydrostatic pressure in portal capillaries which alters vascular pressure gradients. The results of these hemodynamic changes are sinusoidal dilation and leakage of fluid into the interstitial space. Fluid passes through Glisson's capsule when the capacity for lymphatic drainage is exceeded. (30) In conclusion, increased portal pressure and the decreased hepatic perfusion it causes result in cellular damage due to hypoxia. (33)

Chronic changes after blockage that have been described include centrilobular fibrosis which may be seen within weeks, and periportal nodular regeneration, progressive fibrosis and cirrhosis which may not appear for months. (34, 35) It has been postulated that prolonged exposure to hepatotropic substances such as hematopoietins, glucagon and insulin resulting from obstruction combined with

loss of function due to injury to tissue may be one of the mechanisms involved in the genesis of nodular regenerative hyperplasia. (36)

CLINICAL PRESENTATION

Clinically, Budd Chiari Syndrome most often appears as the sudden onset of abdominal pain, ascites and hepatomegaly. (37) A 2013 study by Cheng et. al. showed that 53% of BCS patients had ascites, 31 % had distended abdomens, 28% had hepatomegaly, and 21% suffered abdominal pain. (39) Clinical findings in BCS vary, and patients may experience symptoms months before a diagnosis is made or may present with acute liver failure requiring transplantation before a diagnosis has been made. This catastrophic case is the least frequent presentation. As for the course of symptoms, two studies have shown that half of all BCS patients had symptoms one month before the condition was diagnosed while 14% presented symptoms six months prior to diagnosis. (39)

DIAGNOSIS

Diagnosis of this syndrome is based on clinical findings, medical history, liver function tests and imaging studies. (38)

BCS should be considered in the following situations:

1. Abrupt onset of ascites with painful hepatomegaly
2. Massive ascites with relatively preserved liver function
3. Sinusoidal dilation in liver biopsy in the absence of heart disease
4. Fulminant hepatic failure associated with hepatomegaly and ascites
5. Unexplained chronic liver disease
6. Liver disease associated with known thrombogenic disorder. (38)

Laboratory Tests

Liver function tests include transaminases, bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), albumin, coagulation (PT and PTT), and a platelet count. In BCS, aminotransferases are usually up to 5 times the upper normal limit especially in acute and fulminant forms. Bilirubin and alkaline phosphatase may also rise, but serum albumin may have decrease moderately. (40)

Imaging

Doppler ultrasound

Doppler ultrasound is the imaging study of choice for BCS because it provides qualitative information about the direction and flow pattern. It has a reported sensitivity of 87.5%, (41) and a series of 34 patients by Liao et. al. has reported diagnostic efficacy of 97.1%. (42) According to the Boozari et. al., Doppler ultrasound findings can be classified into specific findings which include thrombosis, stenosis, and fibrotic cord and nonspecific findings which include splenomegaly, heterogeneous hepatic parenchyma, intrahepatic collateral veins, hypertrophy of the caudate lobe, ascites and collateral veins. (43)

Diagnosis of BCS should consider hepatic venous flow and check whether it is absent or retrograde, and whether there are waves of hepatic venous flow that are flat that are associated with reverse flow of the IVC. (44) A series of 9 cases published by Sakugawa and colleagues has shown that the most important ultrasonographic findings for diagnosis of BCS are, in order, occlusion of the hepatic veins, especially of the juxtacaval portion (100%), presence of abnormal intrahepatic and collateral venous structures (89%), segmental obstruction of the IVC (77.8%), prominent lower right hepatic veins (55.6%), and echogenic obstructive membranes (22.2%). (45)

Computed Tomagraphy

In acute BCS, a CT scan will show a pattern of patches with increased enhancement in the central portion of the liver and decreased enhancement in the peripheral region due to portal backflow. Subacute and chronic BCS are characterized by liver atrophy with an enlarged caudate lobe and multiple intrahepatic and extrahepatic collateral veins. (46) In chronic BCS, multiple regenerative hypervascular nodules of sizes varying between 0.5 and 4.0 cm in diameter can be observed. These nodules show an intense and homogeneous enhancement in the arterial phase and remain slightly hyperattentuated in the portal phase. (46, 47)

A study by Vilgrain et. al., of 16 computed tomography images and 20 MRIs concluded that multiplicity (more than 10 nodes) and nodes smaller size than 4 cm are suggestive of benign conditions. (48)

Magnetic Resonance Imaging (MRI)

MRIs of acute and subacute forms of BCS show peripheral areas with low intensity signals on T1 and high intensity signals on T2. In cases of chronic BCS, diffuse atrophy is observed, and there are no significant differences between the peripheral and central zone in both T1 and T2. Regenerative nodules are isointense or hypointense on T2 and are hyperintense on T1. (46, 49) MRI accurately delineates the path of the IVC and hepatic veins and is useful for assessing the extent of membranous obstructions, thrombotic obstructions, and obstructions of collateral veins. (40)

Hepatic Venography, CT Venography (CTV) And Magnetic Resonance Venography (MRV)

Digital subtraction angiography (DSA) is the gold standard for evaluation of the IVC and hepatic veins. This method allows assessment of the level of obstruction, the presence of an occlusive membrane, and differentiation between a thrombus and a tumor. It also allows visualization of intrahepatic and extrahepatic collateral veins. These methods can show the degree to which hepatic veins have been filled in, stenosis in the ostium of the terminal portion, and mays-how a cobweb pattern of collateral veins between the hepatic venules and the systemic veins. (40, 46, 50)

A study by Virmani and colleagues compared VCT with DSAand found an excellent correlation between the two for stenosis detection and classification of the degree and extent of stenosis of the IVC. (51) MRV shows the morphology of an obstruction of the IVC, especially at the distal end of the obstruction with 100% sensitivity, 57.1% specificity, 92.5% positive predictive value and 100% negative predictive value. (52)

HISTOPATHOLOGY

Histological changes can range from severe sinusoidal congestion with inflammation to fibrosis and finally to cirrhosis. (53) In most cases, a liver biopsy will show congestion, loss of liver cells and predominant centrilobular fibrosis. There may also be perivenular fibrosis in diabetic patients and alcoholics. (40) Another histological feature, hepatocellular nodules, shares morphological characteristics with large regenerative nodules, focal nodular hyperplasia and hepatocellular adenomas. Multiplicity, the existence of mixed lesions, potential for hepatocellular regeneration and associated portal obstruction suggest that these nodes are regenerative in nature and conditioned by impaired blood perfusion. (54)

TREATMENT

Treatment for BCS can be divided into medical therapy, radiological procedures and surgical procedures. The therapy of choice depends on the individual clinical and anatomical characteristics. Good clinical outcomes can be obtained as evidenced by the series of Darwish et. al. in which survival the one-year survival rate was 87% and the two-year survival rate was 82% with individualized therapies. The goals of treatment are to prevent thrombus propagation, restore the flow in clogged veins, decongest the liver, and treat and prevent complications related to fluid retention, malnutrition and portal hypertension. (55-56)

Medical Management

Anticoagulation

The first therapeutic measure must be immediate initiation of anticoagulation with low molecular weight heparin followed by vitamin K antagonists with the goal of obtaining an international normalized ratio (INR) of 2 to 3. In addition, oral contraceptives should be suspended. (57-58) It is necessary to monitor platelet counts given the high rates of heparin-induced thrombocytopenia in patients with BCS. (59-60) It is unlikely that anticoagulation by itself will allow for sufficient recanalization of occluded veins or development of adequate circulation to prevent the progression of the disease. However, anticoagulation therapy alone has demonstrated reasonable long-term results in selected patients. (61-62) Medical therapy alone is recommended only for asymptomatic patients who do not have hepatic necrosis and who have normal liver function and easy to manage ascites. (58)

It is important to consider the risks of anticoagulation therapy, especially in patients with current bleeding. It has been shown that esophageal varices are the main source of increased bleeding in patients with BCS anticoagulation. (63) As is routine in cirrhotic patients, screening for esophageal varices, prophylaxis with beta blockers, and endoscopic treatment are recommended. (64).

Thrombolysis

The evidence regarding thrombolytic therapy is scant and limited to small case series and individual reports. Systemic and locally administered thrombolytic agents have been used, but there are no studies comparing the efficacy and other outcomes according to the route of administration. (65-67) Theoretically local administration allows the use of higher greater concentrations of the drug at the site of action and therefore greater efficacy. The amount of drug administered in local infusions generates coagulopathy comparable to that achieved with systemic administration which means the risks of bleeding is similar for the two methods of administration. There are also no comparisons of different medications, for example a comparison of streptokinase and rtPA, nor are there comparisons of different infusion schemes. A 2004 study published by Sharma et. al. of administration of thrombolysis with rtPA to 10 patients found no benefits for systemic or local administration except for one case of systemic administration in which the outcome was partially successful. This study concluded that thrombolysis is clearly beneficial in recanalization when there has been early detection of a thrombus and thrombolysis procedures are followed by balloon angio-

plasty or stenting of hepatic veins and when thrombolysis is done with short-acting agents. In conclusion, thrombolytic therapy with agents of shorter duration than the rtPA type is recommended without any preference for route of administration, but thromboysis should be followed by interventional procedures. (68)

Prevention and treatment of complications

It is recommended that management of patients with cirrhosis follow clinical practice guidelines. (69)

Radiological Procedures

The ability to access the hepatic venous system intravascularly has allowed for application of minimally invasive procedures to restore venous drainage of the liver. These procedures which include balloon angioplasty, stents and TIPS (transjugular intrahepatic portosystemic shunt) are assuming increasingly important roles for management of patients with recent onset BCS. (70)

Balloon Angioplasty and Stenting

Percutaneous recanalization (angioplasty and/or stent) of the hepatic veins or the IVC should be considered for patients with stenoses of short lengths, and as an adjunct to medical therapy. (71-72). A study by Yang et. al. of 42 patients treated with balloon angioplasty for membranous obstructions of the IVC yielded a success rate of 91% and demonstrated that this technique is an effective treatment measure. (73). A cohort study of 101 patients by Li and colleagues also had a success rate of 91% Permeability at six months was 84%, at 12 months it was 78%, and at 24 months it was 76%. (74) Because reocclusion of affected vessels is a major problem with this therapeutic modality, the use of stents after balloon angioplasty is recommended for maintenance of permeability. (75-76)

A series of 115 patients who had stents placed reported success rates of 87% for stenting of hepatic veins and 94% for stenting of the IVC. Stent permeability at follow-ups of on average 45 months was 96.7% for stents in the IVC and 90.9% for those in hepatic veins. (77) While these techniques have typically been used for acute and subacute forms of BCS, the combination of both seems to be safe and effective for treating chronic BCS with obstruction of the IVC. (78) A new therapeutic strategy of predilatation followed by thrombolysis has been proposed for management of patients with chronic thrombosis of the IVC and has had encouraging results. (79)

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

When the techniques mentioned above fail for clinical or technical reasons, TIPS should be considered. (80) The main justification for the use of this technique is its high efficacy for splanchnic decompression. For this reason, it has been used as emergency and rescue therapy. It is especially useful as a bridge to transplantation for patients with fulminant hepatic failure because it achieves rapid clinical and liver function improvement. (81-83) The results of short-term, medium-term and long-term use of this modality vary. Neumann et. al. studied a series of 14 patients who received TIPS and whose median follow-up time was 50 months, found that none of the patients required transplantation. Ascites control was achieved with marked reduction in the use of diuretics. Only one patient died four years after the procedure as the result of a cause unrelated to BCS. (84) A study by Attwell et. al. of 17 patients treated with TIPS found that 14 (82%) were initially stabilized and the remaining 3 died within the first month. After three years of follow-up only 47% of these patients remained stable, and 23.5% had died. Five patients required restenting because the stent had become occluded, and five underwent transplantation. (85) A study of 124 patients by García-Pagán and collaborators that evaluated long-term outcomes found a one-year survival rate without transplantation of 88%, and a five-year survival rate without transplantation of 78%. (80) In addition to the fact that most patients require reoperation in the first year after insertion, the main risk of this therapy is hepatic encephalopathy. (81)

Surgical Procedures

Surgical management of BCS has evolved over the past three decades. Orthotopic liver transplantation may not be available for all patients, so bridge methods must be considered. These include radiological and surgical shunts. It worth noting that the performance of a surgical portosystemic shunt does not contraindicate future transplantation. (86)

Portosystemic Shunts

Good results have been described with various techniques have including portocavale mesocavale and mesoatriale shunts. The first report of a portocaval shunt dates back to 1948, but this option was only shown to be superior to medical therapy alone thirty years later. (39) The results are encouraging: five-year survived rate reached as high as 90%. (87) A study that included surgical experience with 1,360 patients using different techniques has described a complication rate of 14.8% and a perioperative mortality rate of 3.9%. The success rate was 89.4%, while 6.89% had recurrences. Median follow-up time was 6.8 years. (88)

Portocavales shunts were among the first techniques used with good clinical outcomes and quality of life. (89) A study by Orloff et. al. demonstrated their effectiveness for decompression of portal pressure from 240mm to 7 mm of

saline solution before and after the procedure. The three-year survival rate was 92%, and the 16-year survival rate was 85%. All patients were free of ascites during follow-up and did not require management with diuretics. (90)

Mesocaval shunts have also proven to be successful with reported five-year survival rates of 75%, primary permeability of 70% and secondary permeability of 85%. (56, 91) Mesoatriales shunts, first described in 1978, are another option for patients with IVC obstructions. (92) A study by Chen and colleagues compared long-term use mesoatriale shunts and mesocavoatrial shunts for treatment of combined BCS and concluded that mesocavoatrial shunts result in lower rates of postoperative complications and higher rates of permeability and five-year survival. (93)

Finally, Orloff et. al. reported a prospective study of thirty-eight years of experience with surgical decompression of BCS. This study included 77 patients who were divided into three groups. Group I included 39 patients with isolated hepatic vein occlusion who had been treated with portocavale shunts. Group II had 26 patients with occluded IVCs of whom eight received mesoatrial shunts and the remainder received a combination of portocaval and cavoatrial shunts. Group III included 12 patients with decompensated cirrhosis who had been referred for liver transplantation. Group I had a survival rate of 95% for five to 38 years with 36 patients who had no ascites and who had good quality of life. Group II had a 100% survival rate for five to 25 years, Group III had a 50% survival rate. (94)

Liver Transplantation

Liver transplantationis the best choice for patients who are not candidates for radiological or surgical decompression procedures, for those for whom these methods have failed, and for patients with decompensated cirrhosis or fulminant acute liver failure. (14, 95) According to the analysis of Ratou et. al., patients with ALT levels five times above the upper limit that fall very slowly constitute special group of patients with poor prognoses who may benefit from more aggressive early intervention such as liver transplantation. (96)

The impact of liver transplantation on BCS is difficult to estimate, but various studies have been done of survival rates for this techniquesince the first liver transplantation for this condition was done. (97-99) One study involving 248 patients from 51 European centers showed a one-year survival rate of 76%, a five-year survival rate of 71%, and a ten-year survival rate of 68%. Seventy-seven percent of patient deaths occurred within the first three months, and 47% of these were due to infections. Multiple organ failures due to graft failure or thrombosis of the hepatic artery accounted for 18% of deaths. The only pretransplant predictors of mortality were impaired renal function and histories of shunts. (100) These survival rates are comparable to those found by Ringe et. al. in a series of 43 patients, and similar to the three-year survial rate of 76% reported by Shaked and collaborators. (101- 102). Five-year survival rates of up to 89.4%, and a ten-year survival rates of up to 83.5% have been reported. (103)

The introduction of the MELD score and technological advances in liver transplantation are factors that have had great impacts on patient survival. Transplantation in the era of MELD has been associated with a significantly lower risk of graft loss (hazard ratio [HR]: 0.50, 95% confidence interval [CI], 0.30 to 0.86) of death (HR: 0.52, 95% CI: 0.29 to 0.93) and graft loss within the first 30 days (OR: 0.35, 95% CI: 0.16 to 0.79). Graft survival at 3 years is significantly higher in the MELD era than it was in the pre-MELD era, (68.4% versus 64.5%, p = 0.008). Three year of patient survival rates are also higher in the era of MELD (84.9% versus 72.6%, p = 0.023). (104)

Reocclusion is a latent risk whose occurrence has been observed from 4 months to 7 years after transplantation. It has also been reported that up to 10% of patients may require a new transplant. (105-106) It is precisely for this reason that lifelong anticoagulation is recommended. (105-107)

Laboratory studies have shown a slow progression of liver disease in patients who undergo shunting. In contrast, patients who undergo transplantation maintain higher levels of albumin and have better synthetic functioning. This is why some groups have described treatment algorithms that begin with conservative management and end with transplantation. Periods of up to eight years before transplantation have been reported. (105)

PROGNOSIS

The natural course of this disease has not exhibited good results. It has been estimated that three-year mortality rates for patients suffering from untreated symptomatic forms of the disease is 90%. The prognosis is better for patients with asymptomatic forms of the disease, patients diagnosed early, patients who have low Child-Pugh score lows, patients without ascites of who have easy-to-control ascites, and patients who have low levels of creatinine, sodium, albumin and bilirubin. The main causes of death are liver failure and variceal bleeding. (58, 108) A study by Langlet et. al. showed that 25% of patients diagnosed with BCS died and that the risk of death was higher in the first two years after diagnosis. The prognostic index was based on patient age, Child-Pugh score, ascites and serum creatinine.

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