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Budd- Chiari Syndrome

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ABSTRACT:

World Health organization defined rare diseases as prevalence of 1 or less per 1000 population. Rare diseases are usually genetic and because of this reason these are chronic also. Budd–Chiari syndrome is one of the rare disease. Budd-Chiari syndrome is a congestive hepatopathy caused by blockage of hepatic veins. It involves obstruction of hepatic venous outflow tracts at various levels from small hepatic veins to the inferior vena cava and is the result of thrombosis or its fibrous sequelae. This rare disease is usually caused by multiple concurrent factors, including acquired and inherited thrombophilia. Half of the patients with primary Budd–Chiari syndrome are affected with a myeloproliferative disease.

KEY WORDS: Budd Chiari syndrome; Etiology; Epidemiology; Manifestation; Diagnosis; Treatment.

INTRODUCTION:

Budd Chiari syndrome (BCS) is atypical disease recognized for hepatic venous outflow tract obstruction, with whatever the level of the mechanism of obstruction. Cardiac and pericardial diseases are excluded from this definition as well as sinusoidal obstruction syndrome occurring in the context of an exposure to toxic substances. BCS is further separated into primary BCS when related to a primarily venous disease (thrombosis or phlebitis); secondary BCS when related to compression or invasion by a lesion originating outside the veins (benign or malignant tumor, abscess, cyst, etc.)[1]

George Budd, a British internist, described three cases of hepatic vein thrombosis due to abscess-induced phlebitis in 1845,[2] and Hans Chiari, an Austrian pathologist, added the first pathologic description of a liver with "obliterating end phlebitis of the hepatic veins" in 1899[3].

The classic triad of abdominal pain, ascites, and hepatomegaly is observed in the vast majority of patients with Budd-Chiari syndrome, but it is nonspecific

Patients with acute onset of obstruction typically present with acute right upper quadrant pain. Abdominal distention can also be a significant symptom, because of ascites. Jaundice is rarely observed.

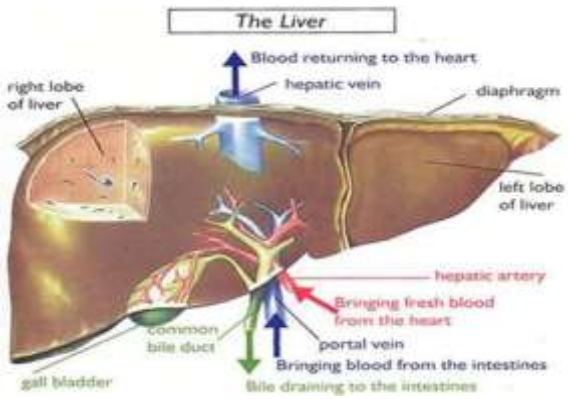

Figure1 Anatomy of Liver showing different sections and veins

BCS varies greatly in terms of its etiology, clinical presentation, and management. The clinical presentation may be asymptomatic, chronic, or fulminant. The treatment strategy varies from medical anticoagulant and antithrombotic.[4, 5, 6]

Etiology

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 tumors or large cysts.[7]

In practice, Budd–Chiari syndrome is regarded as primary when no causes of secondary obstruction are found. Modern imaging techniques allow easy recognition of these associated lesions. Venous compression can be complicated by thrombosis, particularly when prothrombotic factors are present by chance (inherited thrombophilia) or by association (inflammatory response secondary to an adjacent abscess).

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.[8]

Causes of Budd Chiari syndrome:[9,10]
Hematological disorders:
1) Polycythemia Vera (PCV)
2) Myelodysplastic syndrome
3) Essential thrombocythemia
4) Paroxysmal nocturnal hemoglobinuria
5) Hereditary thrombotic disposition
a) Deficiency of vitamin C
b) Deficiency of protein S
c) Thrombophilia Antiphospholipid syndrome
Antiphospholipid syndrome
Pregnancy (after the 3rd trimester of delivery)
Contraceptive pills
Trauma
Membranous obstruction of inferior vena cava
Chronic infections:
1) Tuberculosis
2) Syphilis
3) Aspergillosis
Chronic inflammatory diseases: Malignant diseases

•Hematological disorders:

1. Polycythemia Vera (PCV) or primary polycythemia, or erythraemia, occurs when excess red blood cells are produced as a result of an abnormality of the bone marrow. Polycythemia Vera is classified as a myeloproliferative disease.
2. Myelodysplastic syndrome is another frequent cause of Budd-Chiari Syndrome.This bone marrow stem cell disorder results in disorderly and ineffective hematopoiesis (blood production) manifested by irreversible quantitative and qualitative defects in hematopoietic (blood-forming) cells.
3. Idiopathic thrombocythemia is a rare chronic blood disorder characterized by the overproduction of platelets by megakaryocytes in the bone marrow in the absence of an alternative cause. It belongs to myeloproliferative disorders.
4. Paroxysmal nocturnal hemoglobinuria (PNH) which is a rare, acquired, potentially life-threatening disease of the blood characterized by complement-induced haemolytic anemia due to the appearance of hemoglobin in the urine and thrombosis is another cause of BCS because of the formation of blood clots in the hepatic vein.[11,12,13]
5. Hereditary thrombotic disposition:

a. Deficiency of vitamin C -The hereditary heterozygotic case of the vitamin C deficiency is very often connected with deep venous thrombosis of the lower limb but it is also possible to appear in other venous sites. A considerable amount of patients with vitamin C deficiency remain asymptomatic.
b. Protein S- It is a vitamin k - dependent plasma glycoprotein synthesized in the liver which is present in the circulation in two forms. Deficiency of protein S (hereditary or acquired) is connected with increased risk of thrombosis.
c. Thrombophilia- Thrombophilia is the propensity to develop thrombosis due to an abnormality in the system of coagulation and it is another cause of Budd-Chiari Syndrome. Thrombophilia also includes Factor V Leiden which is the name given to a variant of human factor V that causes a hypercoagulability disorder. In this disorder the Leiden variant of factor V, cannot be inactivated by activated protein C.

•Antiphospholipid syndrome- Antiphospholipid syndrome which is another cause of BCS because of an increased tendency to form abnormal blood clots in blood vessels is

a disorder of coagulation, which causes blood clots in both arteries and veins.

• Pregnancy is a danger factor for thrombosis of hepatic veins and especially after the third trimester of delivery.

• Contraceptive pills can cause severe problems of health in women with of thrombosis of the portal vein, splenic and upper mesenteric vein in women of more than 34 years.

• Trauma can also be a cause but only when it pre-exists a hypercoagulable state.

• Membranous obstruction of inferior vena cava is a reason for chronic hepatic venous stenosis (Asia, India and South Africa)

• Chronic infections such as hydatoid cyst, Aspergillosis, Syphilis, Tuberculosis and amoeboid cyst can also cause mechanical thrombotic or non-thrombotic stenosis of the inferior vena cava.

• Chronic inflammatory diseases such as, Systemic Lupus Erythematosus, Inflammatory diseases of intestine, and Behcet's disease cause non particular superficial phlebitis that reduces the prostaglandin levels which results in thrombosis of hepatic veins.

Epidemiology

Available data are scarce. The prevalence of BCS appears to differ by several orders of magnitude according to the area. In Nepal, BCS represents the leading cause for hospital admission for liver disease, [4] whereas it appears to be very rare in Japan and in France. The level of obstruction might also differ according to the area. As a rule, pure IVC or combined IVC/HV block has predominated in Asia, whereas pure HV block has predominated in Western countries. There was a slight predominance of males, and a median age 45 years in Asia, while there was a marked preponderance of females, and a younger median age (35 years) in the West. Environmental factors such as oral contraceptive use (rare in Asia) and poor nutrition (common in Nepal), have also been incriminated.

Pathogenesis

Blockage of two or more major hepatic veins increases the sinusoidal pressure and reduces sinusoidal blood flow. Obstruction of the hepatic venous outflow tract results in increased hepatic sinusoidal pressure and portal hypertension. 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. Thus, liver congestion, right upper quadrant pain and ascites occur. The ensuing venous stasis and congestion lead to hypoxic damage to adjacent hepatic parenchymal cells. Furthermore, the ischemic injury to the sinusoidal lining cells results in the release of free radicals, and oxidative injury to the hepatocytes ensues. These mechanisms culminate in the development of hepatocyte necrosis in the centri-lobular regions, with progressive centri-lobular fibrosis, nodular regenerative hyperplasia, and ultimately, cirrhosis of the liver. However, if the hepatic sinusoidal pressure is reduced by the creation of a portosystemic shunt or by the development of a portal venous collateral system, liver function improves.

Manifestations and course

The clinical presentation of the Budd–Chiari syndrome depends on the extent and rapidity of hepatic-vein occlusion and on whether a venous collateral circulation has developed to decompress the liver sinusoids. In most cases, the underlying disorders causing thrombosis of the hepatic venous outflow tract are unrecognized at presentation. Presentation ranges from complete absence of symptoms to fulminant hepatic failure, through acute (rapid) or chronic (progressive) development of symptoms over weeks to months before diagnosis is made.

The syndrome can be classified as fulminant, acute, subacute, or chronic.

- Patients with the fulminant form of the syndrome present with hepatic encephalopathy within eight weeks after the development of jaundice. This presentation is uncommon.
- . Patients with the acute syndrome have symptoms of short duration, intractable ascites, and hepatic necrosis without the formation of venous collaterals.
- The subacute form, which is the most common, has a more insidious onset; ascites and hepatic necrosis may be minimal, because the hepatic sinusoids have been decompressed by a portal and hepatic venous collateral circulation.
- When the Budd–Chiari syndrome is acute, thrombosis of all the major hepatic veins is usual

, whereas in the subacute form it is present in only a third of patients

The chronic form is manifested as complications of cirrhosis. Abdominal pain, hepatomegaly, and ascites are present in almost all patients with the Budd–Chiari syndrome. However, asymptomatic patients with hepatic-vein thrombosis have also been described in whom the liver sinusoids were decompressed by large intrahepatic and portosystemic collaterals. Nausea, vomiting, and mild jaundice are more frequent in the fulminant and acute forms, whereas splenomegaly and eso-phagogastric varices may be seen in the chronic forms.

Diagnosis

The diagnosis of Budd–Chiari syndrome should be suspected under the following circumstances:

(a) Whenever ascites, liver enlargement and upper abdominal pain are present simultaneously;

(b) for patients with signs of chronic liver disease, whenever intractable ascites contrasts with mildly altered liver function tests;
(c) whenever liver disease is documented in a patient known to have a prothrombotic disorder;

(d) Whenever fulminant hepatic failure is associated with liver enlargement and ascites;

(e) Whenever chronic liver disease remains unexplained after alcoholism, chronic viral hepatitis B or C, autoimmunity, iron overload and Wilson's disease have been excluded.

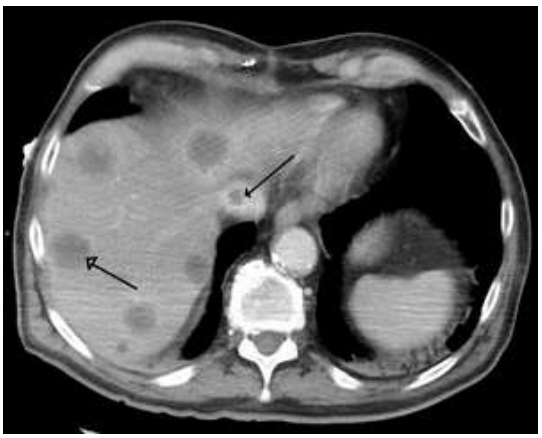

Figure 2 Budd Chiari Syndrome showing clot in inferior Vena Cava

Successive diagnostic (A) and therapeutic (B) steps to be considered for patients with Budd–Chiari syndrome:

Step	A. Diagnostic Method	B. therapy
1.	Doppler- ultrasound	Anticoagulation
2.	Magnetic Resonance Imaging	Angioplasty and Stenting
3.	Venography and Transverse Biopsy	TIPS or Surgical Shunt
4.	Liver Explant	Liver Transplantation

A) Clinical Examination: Clinical examination can reveal the following:

- Jaundice
- Ascites
- Hepatomegaly
- Splenomegaly
- Swelling in hammers
- Venous ulcers
- Appearance of the collateral veins

B) Laboratory Examinations: The examination of ascitic fluid provides useful conclusions for diagnosis:

- Patients usually have high concentrations of protein (> 2g/dL). It is possible not to be present in patients with acute type of Budd – Chiari syndrome.

- White blood cells (WBC) are usually less than 500/ µL.

- The albumin of the ascitic fluid is usually less than 1, 1 (except for the acute types of the disease). The biochemical results of the trial are usually not specific. Mild increases of hepatic enzymes and alkaline phosphatase are present in 25-50% of the patients.

C) Para Clinical Examinations:

- **Doppler ultrasonography** - Doppler ultrasonography of the liver is the technique of choice for initial investigation when BCS is suspected. Imaging 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. Nonvisualized or tortuous hepatic veins are common but nonspecific sonographic findings of BCS, as they may be observed in advanced cirrhosis caused by other etiologies

• **Computerized Tomography**- CT scanning may be recommended for imaging the vascular anatomy and the configuration of the liver when a transjugular intrahepatic portosystemic shunt is considered. Nonvisualized hepatic veins are suggestive of disease on CT, but false-positive or indeterminable results can occur in 50% of cases.

• **Magnetic resonance Imaging** (MRI) is an examination that provides useful images for the evaluation of hepatic venous flow. The sensitivity and specificity is 90%.

• **Hepatic Venography** is a specific examination where clots of blood are observed in the hepatic veins, while hepatic vein orifices cannot be cannulated.

• **Liver Biopsy Histological findings**: The pathological conclusions after the biopsy of the liver are: 1) acute venous fluxion and central lobe atrophy of liver cells and 2) clots of blood inside the final hepatic venules. The severity of the disorder can be determined by conclusions from biopsies.

Treatment

Therapeutic approaches to treat BCS are diverse and should be adapted depending on disease severity. The step-wise approach for treating BCS is; 1. Anticoagulation, 2. Angioplasty and stenting, 3. TIPS or surgical shunt, and 4. Liver transplantation.

Anticoagulation therapy

Anticoagulation therapy should immediately be started even for asymptomatic patients. Although specific therapy for underlying prothrombotic disease is crucial, Low molecular weight heparin for the initiation of anticoagulation therapy and subsequent long-term anticoagulation with warfarin to achieve an international normalized ratio for prothrombin time of 2.0 to 2.5 are recommended.

Angioplasty and stenting

Catheter-directed thrombolytic therapy, angioplasty, and stent placement may be effective in treating acute BCS. Thrombolytic therapy is considered for patients with the acute form of BCS and especially in rare situations where angiography reveals a fresh thrombus. Urokinase or tissue plasminogen activator (0.5 to 1 mg per hour) is infused directly into the thrombosed hepatic vein for about 24 hours *via* an inserted catheter. Percutaneous or transhepatic angioplasty of localized segments of the narrowed hepatic vein or IVC membranous obstruction may relieve symptoms in more than 70 percent of patients. Short stenosis either of the hepatic veins or of the IVC is found in about a third of patients, and the restoration of outflow through just one of the three main hepatic veins is usually sufficient to relieve symptoms.

Stent insertion may be considered if there is an inadequate response to balloon angioplasty or it may be reserved for cases of recurrent stenosis or occlusion.

Transjugular intrahepatic portosystemic shunt (TIPS) and surgical shunts

For patients presenting weeks to months after hepatic vein thrombosis, the obstruction is generally no longer amenable to thrombolysis or angioplasty. TIPS is recommended as the next step in management. TIPS is useful in patients with an occluded IVC, those in whom the portal vein-IVC pressure gradient is less than 10 mmHg, and those with poor liver function reserve. TIPS is also recommended for those with the acute form of BCS who failed to respond to thrombolytic therapy. TIPS is the most common intervention for BCS, and many studies have reported its high success rate and relatively low rate of complications. Compared to an open surgical shunt, TIPS is associated with lower morbidity and mortality, but its drawback is frequent shunt occlusions requiring repeated interventions. The development of covered stents, however, has significantly improved the patency of TIPS in BCS.

A surgical portosystemic shunt is recommended for patients with the subacute form of BCS when the underlying disease is associated with a favorable long-term outcome, patients have preserved liver function, and a liver biopsy reveals ongoing hepatic necrosis. A pressure gradient between the portal vein and IVC of more than 10 mmHg is associated with a successful long-term outcome. Surgical shunts include a side-to-side portacaval shunt, a central splenorenal shunt, and a mesocaval shunt. The 5-year survival rate after surgical shunting ranges from 75% to 94%, with the higher end of the range being achieved when the IVC is not occluded. The essential aspect is to use a side-to-side portacaval shunt in the early stage of BCS to achieve an excellent outcome for patients with BCS. The rationale for surgical portosystemic shunting is to convert the portal flow into an outflow tract of the liver, and some patients with the severe form of BCS may potentially benefit from this procedure. However, no

studies have described the survival benefit of surgical shunts. In light of advances in the TIPS procedure and accumulated evidence showing the impact of TIPS on patient survival, TIPS is preferred as the first choice for safe and optimal decompression.

Liver Transplantation

In the remaining 10% to 20% of patients with BCS treated with a step-wise management strategy, anticoagulation, angioplasty, and TIPS fail either due to technical failure or to poor clinical results of a technically successful procedure resulting in the need for rescue transplantation. Liver transplantation may also be the treatment of choice in patients with fulminant liver failure and those with highly advanced liver cirrhosis.

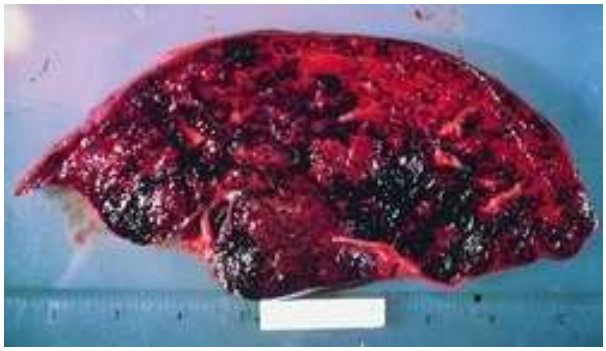

Figure 3 Congestion of Cirrhotic Liver

Conclusion

Budd–Chiari syndrome is an uncommon disorder. Outcome is poor in many cases. Therefore, a successful diagnostic and therapeutic approach is of vital importance. At present many definitions of Budd–Chiari syndrome are used and the distinction between acute and chronic Budd– Chiari syndrome, terms commonly used in clinical practice, is ambiguous. Many diagnostic and therapeutic algorithms applied today are based on personal experience or data from a limited number of patients.

BCS should be treated with a step by step treatment strategy. Physicians should be aware of the diverse etiology of BCS, and first-line therapy should be anticoagulation with medical treatment of the underlying illness (if indicated). Liver transplantation may be indicated as a rescue treatment or for fulminant cases with promising results.

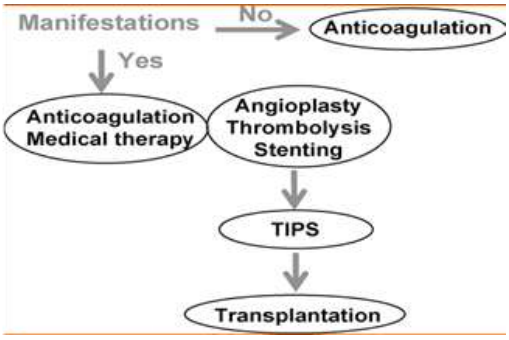

Figure 4[18] Flowchart showing treatment process

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