Review

Budd-Chiari syndrome

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SUMMARY

The Budd-Chiari syndrome is characterized by thrombotic or non thrombotic reduction of the venous hepatic flow. Several works have enabled the comprehension of Budd-Chiari syndrome as well as the diagnosis and treatment. This clinical review attempted to present the Budd-Chiari syndrome overall and more particularly the history, etiology, pathophysiology, diagnosis and the understanding of the latest developments in conservative and surgical management as well as prognosis. This review is based on relevant contributions from general surgery and gastroenterology journals, review articles and international references.

Key words: Liver, portal vein, hepatic venous outflow obstruction, thrombosis, ascites, TIPS

INTRODUCTION

The Budd-Chiari syndrome is characterized by thrombotic or non thrombotic reduction of the venous hepatic flow. These two types of reduction in the venous hepatic flow often occur between the right lobular hepatic vein and the ligament of the inferior vena cava of the right hepatic lobe. In the United States of America Budd-Chiari syndrome appears rarely, but its exact frequency is unknown.

Internationaly: Budd-Chiari syndrome is also rare but it appears more frequently in countries of Asia. The syndrome appears in all human and all nations between the

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age of 30 and 40 years old, although it can exist is older of younger age groups.

Historical and epidemiologic evidence

George Budd was the son of the surgeon Samuel Budd at North Taunton, known for his article on an outbreak of typhoid fever in their native village. His first position was in the navy hospital of Dreadnaught, where he studied plenty of cases from sailors, who suffered from their liver, when they returned back home and there he based his studies on the structure of liver diseases. He described the syndrome in the year 1845.[1] Hans Chiari was born in Vienna the 1851 and was the son of an obstetrician called Johann Chiari (1817-1854). He studied medicine in Vienna and in the year 1874-1875 he was assistant of the famous Karl Freiherr von Rokitansky from where they studied and referred to the appearance of the syndrome that leads from the liver cirrhosis and ascites and results in the destruction of hepatic veins because of clot or mass.[2,3]

Etiology

Most patients have a predisposition for thrombosis. In one third of the patients the cause is not visible. Causes of Budd-Chiari syndrome include[4,5]: (Table 1)

- Hematological disorders:

- 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. The most significant characteristic of this illness is an absolute increase of red blood cells because of the uncontrollable production of them. This is accompanied by the increased production of the megakaryocytic, medullar class which has as a result the increase of white and red blood cells and platelets also. This attributes to an irregular clone of the hemopoetic stem cells with rising sensitivity of the different growth factors.[6]

Table 1. Causes of Budd-Chiari syndrome.

Hematological disorders:

1) Polycythemia Vera (PCV)

2) Myelodysplastic syndrome

3) Essential thrombocytemia

4) Paroxysmal nocturnal hemoglobinuria

5) Hereditary thrombotic disposition

a) Deficiency of vitamin C

b) Deficiency of protein S

c) Thrombophilia

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

- Myelodysplastic syndrome is another frequent cause of Budd-Chiari Syndrome.This bone marrow stem cell disorder results in disorderly and ineffective haematopoiesis (blood production) manifested by irreversible quantitative and qualitative defects in hematopoietic (blood-forming) cells. The median age at diagnosis of a MDS is between 60 and 75 years old. Signs and symptoms are nonspecific and generally related to the blood cytopenias: Anemia, Neutropenia, and Thrombocytopenia.

- 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. Continuous multiplication of megakaryocytes leads to an increase of platelets in circulation. It is also characterized from platelet count more than 600,000/mm3, megakaryotic hyperplasia splenomegaly and a clinical class of signs resulting from bleeding and thrombosis.

- Paroxysmal nocturnal hemoglobinuria (PNH) which is a rare, acquired, potentially life-threatening disease of the blood characterised by complement-induced haemolytic anaemia (anaemia due to destruction of red blood cells in the bloodstream), due to the appearance of haemoglobin in the urine and thrombosis is an-

other cause of BCS because of the formation of blood clots in the hepatic vein.[7-9]

Hereditary thrombotic disposition:

1. Deficiency of vitamin C or a deficiency of the anticoagulant mechanism is combined with a fluxionary increased danger of thrombosis in the rare hereditary homozygote or heterozygote composition. The deficiency of vitamin C is related to life-threatening acquired fetal porphyria or hefty venous thrombosis. 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.

2. Protein S is a vitamin K - dependent plasma glycoprotein synthesized in the liver. In the circulation, Protein S exists in two forms: a free form and a complex form bound to complement protein C4b. The most significant function of protein S is to act as a cofactor to Protein C in the inactivation of Factors Va and VIIIa. Deficiency of protein S is connected with increased risk of thrombosis. Deficiency of protein S can be hereditary or acquired. The latter is commonly attributed to liver diseases or deficiency of vitamin K. Deficiency of vitamin S often shows clinically venous thrombo embolism (VTE).Connection of protein S deficiency with arterial thrombosis appears to be symptomatic or asymptomatic. Arterial thrombosis is not visible with other hereditary disorders of anticoagulants (for example deficiency of protein C or Antithromvin III, factor B mutation of genes of Leiden).[10-14]

3. 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. Hereditary defects in one or more of the clotting factors can cause the formation of potentially dangerous blood clots. 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. Factor V Leiden mutation is the most common hereditary hypercoagulability disorder amongst Eurasians. 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.[15,16]

- 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 woman 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 preexists a hypercoagulable state.[17,18]

- 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.[19]

- Chronic inflammatory diseases such as Sarkoidosis , Systematic Lupus Erythimatosous, Inflammatory diseases of intestine, Sjogrens syndrome and Behcets disease cause non particular superficial phlebitis that reduces the prostaglandin levels which results in thrombosis of hepatic veins.[20]

- Malignant diseases such as hepatocellular carcinoma, atrial myxoma, Liomyosarcoma and Wilms tumor, kidneys and adrenal glands cancer can also cause thrombosis or stenosis of hepatic veins.[21,22]

Phathophysiology:

Budd – Chiari syndrome includes any obstruction of the venous vasculature of the liver from the venules to the right atrium. This leads to increased portal vein and hepatic sinusoid pressures as the blood flow stagnates. The increased portal pressure causes: 1) increased filtration of vascular fluid with formation of protein-rich ascites and 2) collateral venous flow through alternative veins leading to gastric varices and hemorrhoids. Obstruction also can lead to hepatic necrosis and eventual centrilobular fibrosis due to ischemia.

Clinical Types:

The classical term is abdominal pain, ascites and hepatomegaly which is observed in the great majority of patients and is asymptomatic. An elevated index of suspicion is required for diagnosis. Four main clinical variations have been described: acute disease of the liver, sub acute disease of the liver, fulminant disease of the liver and liver decompensation. The most common type is the sub acute which is complicated by portal hypertension and variable degrees of liver decompensation.

- Acute and sub acute type: These patients are characterized the rapid development of the abdominal pain, ascites, hepatomegaly, jaundice and reduction of kidney function.

- Chronic type: This is the most common type of presentation. Patients appear with progressive ascites. Jaundice is absent and nearly 50% of the patients also have problems in kidneys function.

- Fulminant type: is unusual, the fluminant or sub fluminant liver decompensation appears with ascites, tender hepatomegaly, jaundice and reduction of kidney function.

Diagnosis:

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 ascetic 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 ascetic 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 alcaline phosphatase are present in 25-50% of the patients.

Hematological studies are needed to evaluate for hypercoagulability.

C) Para Clinical Examinations:

- Ultrasonography(U/S)

1. Clots of blood can be depicted.

2. The Triplex ultrasound is the examination of choice. The sensitivity and specificity is 85-90%.

The frequent non-specific signs are splenomegaly (78%), unhomogeneous liver parenchyma (76%), intrahepatic collaterals (73%), caudate lobe hypertrophy (67%),

ascites (56%) and extrahepatic collaterals (44%). These are sonomorphological signs in BCS. The combination of ultrasound signs: altered hepatic and/or caval veins and caudate lobe hypertrophy, is a good strategy to diagnose BCS. Patients with portal vein thrombosis or portal hypertension have a poor prognosis.[23-25]

- Computerized Tomography (C.T.) can be used as a method for intervention procedures like biopsies.[26,27]

- 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

Optimal management requires that treatment should be guided by the predominant clinical symptoms (liver failure or portal hypertension) and anatomical considerations should always be taken into account surgical risk (Table 2).

Conservative treatment:

Observation of the patient with frequent gastroscopies for esophageal and gastric varices is needed. As a precaution β-blockers can be administered. The electrolyte levels also must be observed because of the application of diuretics. Another parameter that must be measured is APTT and PT for precaution from bleeding.[28]

1. Treatment of ascites

2. Anticoagulant treatment for prevention of recurrent and ongoing thromboembolic occlusion.

- Warfarin is an inhibitor of vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. Common clinical indications for warfarin use are deep venous thrombosis, pulmonary embolism and other thromboembolic disorders.

Table 2. Treatment of Budd-Chiari Syndrome

Conservative treatment:
1) Treatment of ascites
2) Anticoagulant treatment
3) Fibrinolytic agents
Surgical treatment:
1) Portal venous decongestion
2) Hepatoarterial anastomosis
3) Orthotopic liver transplanation
Interventional radio therapy: Transjugular intrahepatic portosystemic shunt (TIPS)

The target INR level will vary from case to case depending on the clinical indicators, but tends to be 2–3 in most conditions.

- Acenocoumarol (Sintrom): which is an anticoagulant that functions as a vitamin K antagonist like warfarin and is a derivative of coumarin.

3. Fibrinolytic agents which are used to dissolve a pathologic intraluminal thrombus or embolus that has been broken down by the process of fibrinolysis. It is also used for the prevention of recurrent blood clot formation and the rapid restoration of hemodynamic disturbances such as in myocardial infarction, ischemic stroke, massive pulmonary embolism, acute limb ischemia.

Streptokinase (Kabikinase, Streptase): by activating plasminogen through cleavage to produce plasmin. Plasmin is produced in the blood to break down the major constituent of blood clots, fibrin, therefore dissolving clots once they have fulfilled their purpose in stopping bleeding. Extra production of plasmin caused by streptokinase breaks down unwanted blood clots.

Urokinase (Abbokinase): is a direct plasminogen activator which converts plasminogen to the enzyme plasmin resulting in the degradation of fibrin clots, fibrinogen and other plasma proteins. Urokinase is used clinically as a thrombolytic agent in the treatment of massive deep venous thrombosis, pulmonary embolism, myocardial infarction and occluded intravenous or dialysis cannulas. It is also administered intrapleurally to improve the drainage of complicated pleural effusions and empyemas.

Alteplase (Activase): is a tissue plasminogen activator that is used in diseases that feature blood clots, such as pulmonary embolism, myocardial infarction and stroke. To be effective, tPA must be administered within the first three hours of the event given intravenously, or within six

hours to be administered through an arterial catheter directly to the site of occlusion.

Anistreplase (Eminase): converts plasminogen to plasmin, which in turn degrades fibrin (blood clots) to fibrin split products.

Surgical treatment:

It depends on the reduction of liver function and also from the anatomic structure of the liver. Recently some references showed us that survival of the patients that were surgically treated was better than in those cases where conservative treatment was used.[29-31]

- Portal venous decongestion: This method is used in acute phase cases, whereas in chronic cases of Budd-Chiari syndrome it is more frequently treated with liver transplantation because of liver cirrhosis (OLT). In specialized centers there is a rate of up to 90% of success when there is absence of portal vein corrosion and an end to end anastomosis of portal vein is used. If corrosion of the portal vein exists then another method is used which is the combination of portal vein with anastomosis of the superior mesenteric vein. Nowadays a combination of anastomoses of portal vein with mesenteric or jugular vein is used.

- Hepatoarterial anastomosis: Hepatoarterial anastomosis and its alternative femerofemoral by-pass and reconstruction of portal vein are frequently used. They are progressive interventions which give very good lasting results.

- Interventional Radio therapy:
Transjugular Intrahepatic Portosystemic Shunt (TIPS): The procedure of setting communication of the by-pass is made between the right arm of hepatic vein, the portal vein and usually from the inner side of jugular vein. Technically the most difficult part of the TIPS procedure is the puncture of portal vein. Many methods been tried for the accomplishment of this including the purpose and ultrasonography. General anesthesia is not needed. The percentage of success of this method is from 94-100%. A common complication is hepatoencephalopathy in 25% and also the constriction of anastomoses which appears in 34% to 75% of patients. TIPS method can also be used in children, but this procedure is more difficult including the use of renal and coronary arteries. Small series of Budd-Chiari Syndrome (BCS) patients indicate that TIPS may be useful. However, the influence of TIPS on patient survival and factors that predict the outcome of TIPS in BCS patients remain unknown. Long-term outcome for pa-

tients with severe BCS treated with TIPS is excellent even in high-risk patients, suggesting that TIPS may improve survival. Furthermore, studies have shown that a small subgroup of BCS patients with poor prognosis despite TIPS mey benefit from early orthotopic liver transplantation (OLT).[32,33]

COMPLICATIONS:

- Secondary complications of the liver because of liver function failure.

- Hepatic encephalopathy.

- Bleeding of varicose veins.

- Hepatorenal syndrome.

- Portal Hypertension.

- Secondary complications because of over bleeding.

PROGNOSIS:

- The natural development of the disease does not have good results. The following factors are related with better prognosis.

  - Diagnosis in young age

  - Low Child-Pugh score

  - Absence of ascites or easily controlled ascites

  - Low levels of creatinine, sodium, albumin bilirubin.

- The formula that has been proposed for calculating the prognostic levels is when the score is less than 5.4 and has been related with a good prognosis. The formula that calculates the prognosis is the following:
Index of prognosis = (ascites score x 0.75) + (Pugh score x 0.28) + (age x 0.037) + (levels of creatinine x 0.0036).

- Prognosis is low in patients that suffer from Budd-Chiari Syndrome and remain incurable. Death comes from gradual reduction of liver function within 3 months to 3 years from diagnosis. The 5-year survival is calculated at 38-87% following systematic by-pass of portal vein. The actual 5-year survival percentage after the transplantation of liver is 70%.[34,35]

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