INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare, heterogeneous, and potentially lethal condition related to the obstruction of the hepatic venous outflow tract at any level from the small hepatic veins to the junction of the inferior vena cava with the right atrium ***(Valla, 2003).***

BCS occurs in approximately 1/100000 of the general population worldwide ***(Valla, 2003).*** It is considered primary or secondary depending on the origin of the obstructive lesion. If obstruction is the result of endoluminal venous lesion-like thrombosis, primary BCS is considered. In secondary BCS, the cause originates from neighboring structures like extrinsic compression or tumor invasion ***(Aydinli and Bayraktar, 2007).***

Ultrasound combined with Doppler imaging has a diagnostic sensitivity of more than 74% and should be the first line of investigation ***(Gupta et al., 1987 and Millener et al., 1993).***

When it is difficult to obtain an adequate sonographic evaluation or when the diagnostic features cannot be demonstrated, computed tomography or preferably MRI should be performed as a second line of investigation ***(Kage et al., 1992 and Millener et al., 1993).*** With the combination of these imaging studies, the diagnosis will remain uncertain only in a small minority of cases.

Third line of investigation should be Inferior venacavography or hepatic venacavography which may show "Spider web" pattern of hepatic venous collaterals, Thrombus in hepatic veins or IVC or Long segmental compression of IVC ***(Valla, 2009).***

HCC is considered the 5th most prevalent cancer in the world causing 300,000- 500,000 deaths per year. Over the last 5 to 8 years evidence has been accumulating in different countries that the incidence of hepatocellular carcinoma (HCC) is rising ***(Liu and Kao, 2008 and Su et al., 2008).***

The major risk factors for HCC are chronic hepatitis B (HBV) or C (HCV) virus infection, alcohol, hereditary haemochromatosis, diabetes and cirrhosis regardless of cause ***(Di Bisceglie et al., 1998).***

In BCS patients, HCC appears to be as significant as a long-term complication as it is in other chronic liver diseases. Serum alpha fetoprotein appeared to be more specific for a diagnosis of HCC in patients with BCS than with other liver diseases. Patients with long-standing IVC obstruction carried a risk of developing HCC that was 70-fold higher than those with pure hepatic vein involvement ***(Valla, 2009).***

BCS accounts for 0.7% of all cases of HCC ***(Takayasu, et al., 1994).*** Many cases of BCS complicated with HCC have been reported with some variation ranging from 6.4 to 47.5%

(Kew et al., 1989, Nakamura et al., 1968 and Okuda et al., 1995).

Until now, the accurate pathogenesis of HCC in BCS has not been elucidated yet**.** The chronic liver injuries and congestion caused by obstruction of hepatic venous outflow might contribute to a fibrotic process and development of nodular type of HCC ***(Gwon et al., 2010).***

Prolonged congestion can lead to hepatocyte necrosis, and its replacement with fibrous tissue results in fibrosis, which is assumed to be the mechanism of cirrhosis and HCC development ***(Gwon et al., 2010)***.

This hypothesis is supported by frequent findings of liver parenchymal cirrhotic changes adjacent to HCC in BCS context ***(Moucari et al., 2008).***

The aetiology of HCC arising in patients with BCS has not been clearly identified. It is believed that, due to hepatic venous outflow obstruction hepatic congestion with extensive centrilobular necrosis and subsequent liver fibrosis can increase hepatic regenerative activity; thereby increasing DNA synthesis, this may play a part in hepatocarcinogenesis. Most cases of HCC are associated with IVC thrombosis but rare in 1ry hepatic vein thrombosis ***(Okuda et al., 1998 and Vilgrain et al., 1999).***

AIM OF THE WORK

To study the frequency, sociodemographic features, risk factors and relevant characteristics (clinical, laboratory & imaging) of hepatocellular carcinoma in primary BCS in a cohort of Egyptian patients who were presented to the EASVLD and Tropical Medicine Department, Ain Shams University hospitals.

Chapter (1)
BUDD- CHIARE SYNDROME

Anatomical Aspects of the Liver

Segmental anatomy of the liver:

The liver is one of the largest organs in the body, representing 2% of the total body weight ***(Gerard and Doherty, 2010)***.

The liver is divided into eight segments based on the branching of the portal triads and hepatic veins, with the caudate lobe designated as segment I. Segments I-IV comprise the left liver, and segments V-VIII, the right***(Sleisenger and Fordtran's, 2010).***

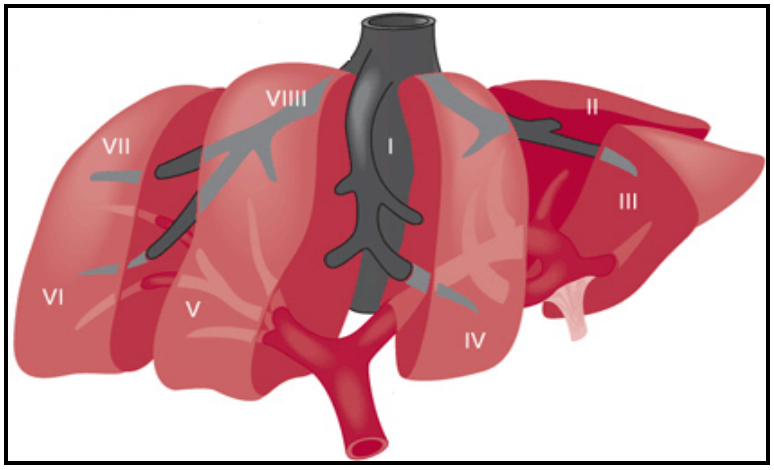

Fig. (1): Segmental anatomy of the liver
(Sleisenger and Fordtran's, 2010).

Vascular Anatomy of the Liver

Hepatic Artery

The liver has a dual blood supply consisting of the hepatic artery and the portal vein. The hepatic artery delivers approximately 30% of the blood supply and 60& of its oxygen demand, and the portal vein approximately 70%. The common hepatic artery arises from the celiac axis (trunk), as well as the left gastric, a splenic artery ***(Charles and Brunicardi, 2010)***.

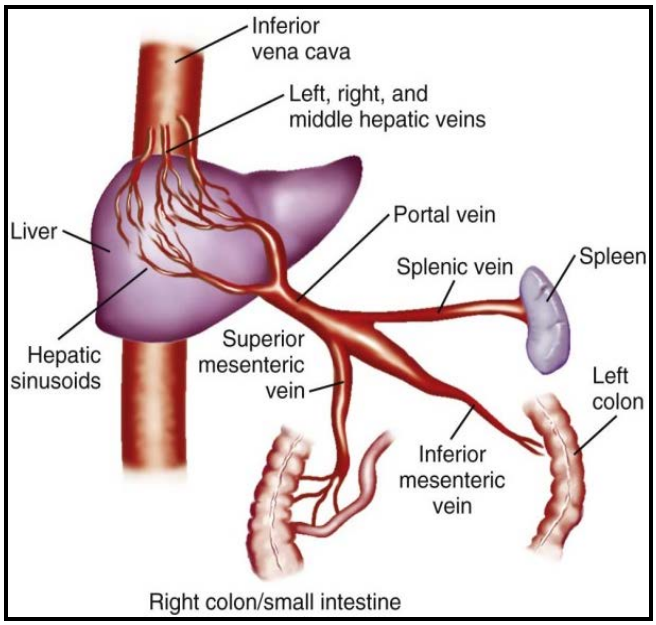

Fig. (2): Vascular anatomy of the liver ***(Gerard and Doherty, 2010)*.**

Portal Vein

The portal vein is formed by the confluence of the splenic vein and the superior mesenteric vein. The portal vein

drains the splanchnic blood to the liver before returning to the systemic circulation ***(Charles and Brunicardi, 2010).***

Hepatic Veins

There are three hepatic veins (right, middle, and left) that pass obliquely through the liver to drain the blood to the suprahepatic IVC and eventually the right atrium ***(Charles and Brunicardi, 2010)***.

The caudate lobe is unique because its venous drainage is directly into the IVC. In addition, the liver usually has a few small, variable short hepatic veins that directly enter the IVC from the undersurface of the liver ***(Charles and Brunicardi, 2010)***.

Histological aspects of the liver

The functional unit of the liver is the acinus. The human liver contains about 100,000 acini ***(Dooley et al., 2011).***

Each acinus is at the end of a vascular stalk containing terminal branches of portal veins, hepatic arteries, and bile ducts. This is why the central portion of the acinus, sometimes called zone 1, is well oxygenated, the intermediate zone (zone 2) is moderately well oxygenated, and the peripheral zone (zone 3) is least well oxygenated and most susceptible to anoxic injury ***(Dooley et al., 2011).***

Blood flows from the center of this functional unit to the central veins which coalesce to form the terminal branches of the hepatic veins at the periphery, which drain into the inferior vena cava ***(Dooley et al., 2011).***

Definition of BCS

Budd-Chiari syndrome (BCS) is a clinical condition caused by hepatic venous outflow obstruction located anywhere from the small hepatic veins to the junction of the inferior vena cava and the right atrium, regardless of the cause of the obstruction ***(Hong et al., 2010).***

Classification

BCS can be 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 ***(Janseen et al., 2003).***

Epidemiology of BCS:

BCS has a prevalence of 1.4 per million individuals in Western countries and 2.4 per million in Japan ***(Valla, 2009)***.

In Western countries, most BCS patients are females, whereas in Asia the male to female ratio is close to 1, with a slight bias towards the male gender ***(Valerioand Ida, 2010).*** Most affected Western patients have been young females whereas in Asia, middle-aged patients of either sex were predominantly affected ***(Darwish et al., 2007).***

Pathology of BCS

The parenchymal hepatic damage and the histological abnormalities are variable, depending on the acuity and extent of hepatic venous outflow obstruction ***(Bayraktar, et al., 2007).***

The obstruction of a single main hepatic vein is clinically silent ***(Valla, 2002).*** The obstruction of two or three main hepatic veins produces two hemodynamic changes: an increased sinusoidal blood pressure and a reduced sinusoidal blood flow ***(Henrion, 2000).***

In chronic disease, direct blood flow from the caudate lobe to the IVC compensates for hepatic outflow obstruction. Over time, the caudate lobe becomes hypertrophic while cirrhosis and atrophy develops in the rest of the liver ***(Olzinski and Sanyal, 2000).***

The hepatocellular carcinoma is associated with BCS by two mechanisms; Hepatocellular carcinoma can cause hepatic vein or inferior vena cava (IVC) obstruction by direct vascular invasion of the tumor, resulting in secondary outflow occlusion. Alternatively, hepatocellular carcinoma can develop de novo in patients who have BCS and cirrhosis ***(Takayasu et al., 1994).***

Etiology of BCS

Etiology of primary BCS (an overview):

Intravascular thrombosis, mostly seen in primary myeloproliferative disorders, is the most common mechanism leading to the obstruction of the hepatic venous system. At least one hereditary or acquired procoagulative disorder can be identified in 75% of patients with BCS ***(Valla, 2002).***

Polycythemia Vera is found in between 10%-40% of patients, whereas essential thrombocythemia and myelofibrosis are less prevalent causes ***(Valla et al., 1985 and Denninger et al., 2000).***

As many as 30% of all cases of BCS are found to have factor V Leiden mutation (FVLM) which is present in the majority of pregnancy- or oral contraceptive-related cases of hepatic vein thrombosis ***(Deltenre et al., 2001).***

Although less common in western countries, primary membranous obstruction of the inferior vena cava (IVC) is the most common cause of BCS in South Africa and Asia, and is thought to be a consequence of IVC thrombosis ***(Okuda, 2002).***

For unknown reasons, 45-50% patients with known membranous occlusion of IVC ultimately develop hepatocellular carcinoma (HCC), even in the absence of cirrhosis ***(Simson, 1982).*** On the other hand, HCC has not been reported to be a

complication of hepatic vein thrombosis, except in Behcet's disease-associated BCS ***(Bayraktar et al., 1998).***

In about 10% of patients with BCS, an underlying aetiology cannot be identified ***(Denninger et al., 2000).***

Table (1): Causes of BCS ***(Bayraktar et al., 2007).***

Common causes

- **Hypercoagulable states:**

1) Inherited thrombophilic disorders

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden mutation
- Prothrombin gene mutation

2) Acquired procoagulative disorders

- Antiphospholipid syndrome
- Myeloproliferative disorders (overt and occult)
- Paroxysmal nocturnal hemoglobinuria
- Cancer
- Pregnancy
- Use of oral contraceptives

Uncommon causes

- Tumoral invasion **(secondary BCS)**
- Hepatocellular carcinoma **(secondary BCS)**
- Renal cell carcinoma
- Adrenal carcinoma
- Aspergillosis **(secondary BCS)**
- Behcet's syndrome
- Inferior vena caval webs
- Trauma
- Inflammatory bowel syndrome
- Idiopathic

Causes of Inherited Thrombophilia

(1) Factor V Leiden mutation (FVLM):

The most common cause of inherited thrombophilia is FVLM. This mutation was first defined by ***Bertina et al*** in ***(1994),*** after studies of ***Dahlback and colleagues, (1993)*** that showed a resistance factor against activated protein C (APC)

The diagnosis of FVLM depends partially on the activated protein C resistance (APCR) as a screening tool but direct PCR test to detect mutation can also be applied ***(Greer et al., 1998)***.

(2) Protein C (PC) and protein S (PS) deficiency:

PC is synthesized in liver by a vitamin K dependent mechanism. During coagulation cascade, this protein is activated by thrombin into its active form, namely activated PC (APC) ***(Kottke-Marchant and Comp, 2002).***

The PC activity is usually determined by functional tests. The heterozygote PC deficiency reveals itself by PC activity less than 50%, whereas in homozygote deficiency PC activity is below 5% ***(Colman et al., 2001).***

PS is naturally a cofactor of activated PC during inactivation processes of activated factors V and VIII. This protein is synthesized from liver, endothelial cells, megakaryocytes and in testis by vitamin K dependent reactions ***(Bayraktar and Harmanci, 2006).***

The protein S deficiency is accepted as a weak risk factor for thrombosis formation which is about 2 times more than normal population ***(Bayraktar and Harmanci, 2006).***

(4) Hyperhomocysteinemia (HH):

HH is well known to cause venous and arterial thromboembolism ***(Wuillemin and Solenthaler, 1999).*** Methylenetetrahydro-folate reductase (MTHFR) is an enzyme in the remethylation pathway of homocysteine. Deficiencies in this enzyme lead to HH ***(Frosst et al., 1995).***

Hyperhomocysteinemia, especially when assoc-iated with factor V Leiden mutation, is a newly recognized risk factor for the development of BCS and these two factors should be investigated in all patients with the syndrome ***(Colak et al., 2006).***

Causes of Acquired Thrombophilia

(1) Antiphospholipid syndrome (APS):

The Antiphospholipid Syndrome (APS) is a form of acquired, autoimmune thrombophilia. It is associated with significant morbidity and mortality in the form of thrombotic events and pregnancy loss. Antiphospholipid syndrome is diagnosed in a patient suffering venous or arterial thrombosis and/or pregnancy failure, in whom characteristic laboratory abnormalities are detected: typically Lupus Anticoagulant (LA)

or IgG/IgM Anticardiolipin Antibodies (ACA) ***(Robertson and Greaves, 2006).***

(2) Myeloproliferative disorders (MPDs)

Myeloproliferative disorders (MPDs) are a heterogeneous group of disorders characterized by cellular proliferation of one or more hematologic cell lines in the peripheral blood, distinct from acute leukemia***(Rasool and Groshek, 2008).***

Table (2): French-American-British (FAB) and World Health Organization (WHO) classification of MPDs ***(Rasool and Groshek, 2008).***

FAB	WHO
Chronic myelogenous leukemia	Chronic myelogenous leukemia
Polycythemia vera	Polycythemia vera
Essential thrombocythemia	Essential thrombocythemia
Agnogenic myeloid metaplasia/ myelofibrosis	Chronic idiopathic myelofibrosis
	Chronic neutrophilic leukemia
	Chronic eosinophilic leukemia/ hypereosinophilic syndrome

Role of JAK_2 mutation in MPDs and BCS:

MPDs account for about 50% of BCS patients ***(Mercieret al., 2007).*** A recent, crucial, advance in the field of chronic MPD has been the identification of a particular somatic mutation (V617F) in the Janus tyrosine kinase-2 (JAK_2) gene in myeloid cells ***(James et al., 2005).*** JAK_2 is coupled to the growth factor receptor on the cells of the myeloid lineage.

Activation by the ligand (erythropoietin, thrombopoietin or other growth factors) elicits the signal for proliferation and differentiation of the myeloid precursors into mature cells through JAK_2 phosphorylation. (V617F) JAK_2 mutation produces constitutive activation of signal transduction resulting in hypersensitivity to growth factors. This single somatic mutation can be detected in granulocytes or other blood cells of the myeloid lineage ***(Valla, 2009).***

V617F JAK_2 has been found in about 80% and 50% of patients with polycythemia Vera, and essential thrombocythemia or idiopathic myelofibrosis, respectively ***(Hussein et al., 2007).***

The clusters of dystrophic megakaryocytes at bone marrow biopsy proved recently to be a specific feature for MPD ***(Chait et al., 2005).*** About 80% of BCS patients with a MPD harbour V617F JAK_2 mutation ***(Kiladjian et al., 2006).***

In the remaining patients, evidence for the underlying MPD is derived from bone marrow biopsy findings.. Peripheral blood cell counts remain within normal values in most patients with MPD when BCS is present, due to hypersplenism, hemodilution and iron deficiency***(Valla, 2009).***