Introduction

Esophageal variceal bleeding (EVB) is a potentially deadly complication in patients with liver cirrhosis and portal hypertension ***(Brandenburger and Regenstein, 2002; Bhasin and Malhi, 2002).*** In patients with cirrhosis, the incidence of esophageal varices ranges from 35% to 80% and approximately a third of patients with esophageal varices (EV) experience variceal bleeding, and up to 70% of the survivors have one or more additional episodes of bleeding ***(Tsokos and Turk, 2002).***

The risk of variceal haemorrhage is clearly related to the size of EV. Therefore primary prevention of variceal bleeding applies to patients with previously diagnosed large EV (grade II or III) detected by periodical upper GIT endoscopy ***(Lebre et al., 2005).***

A generalized program of periodical upper gastrointestinal tract endoscopy in these patients might result in heavy economical burden even for developed countries ***(Spiegel et al., 2003).***

In order to reduce the increasing burden that endoscopy units will have to bear, some studies have attempted to identify characteirstics that non-invasively perdict the presence of EV such as right live lobe diamter/serum albumin, and platelet count/spleen size ratio ***(Thomopoulos et al., 2003)***.

It was previously reported that cirrhotic patients with platelet count of <88.000 were five times more likely to have

large EV ***(Zaman et al., 1999).*** Another study done by ***Gue et al. (2004)*** showed that thrombocytopenia and leucopenia can be used to stratify risk for occurrence of esophageal varices in cirrhotic patients.

Aim of the Work

The aim of this study is to determine the senstvity and specificity of leucopenia and thrombocytopenia as non-invasive markers for EV detection and bleeding.

Liver Cirrhosis

Definition:

Cirrhosis is a slowly progressive disease, causing irreversible scarring and nodularity of the liver in response to chronic injury from a variety of causes. This process distorts the normal liver architecture, interferes with blood flow through the liver and disrupts the functions of the liver ***(Mathews et al., 2006).***

Fibrosis previously was thought to be an irreversible scarring process formed in response to inflammation or direct toxic insult to the liver, but current evidence suggests that fibrosis may be reversible in some patients with chronic hepatitis B after antiretroviral therapy ***(Malekzadeh et al., 2004).***

Any chronic insult to the liver can cause progression to cirrhosis. Although numerous pathophysiologic mechanisms of injury exist, the final common pathway is persistent wound healing resulting in hepatic parenchymal fibrosis. In most persons, approximately 80 to 90 percent of the liver parenchyma must be destroyed before liver failure is manifested clinically. When complications of cirrhosis occur, they typically are related to impaired hepatic function or actual physical disruption and reorganization of the liver parenchyma ***(Friedman and Schiano, 2004).***

Etiologies of Hepatic Cirrhosis:

Single or multifactorial insults to the liver ultimately lead to cirrhosis, the most common being alcohol abuse, chronic hepatitis

C, and obesity with concomitant nonalcoholic fatty liver disease NAFLD ***(Friedman and Schiano, 2004 and Crawford, 2005).***

Most common causes:

Chronic hepatitis B or C, alcohol, biliary obstruction, biliary atresia/neonatal hepatitis, congenital biliary cysts, cystic fibrosis, Primary or secondary biliary cirrhosis hemochromatosis, NAFLD - most commonly resulting from obesity; also can occur after jejunoileal bypass.

Less common causes:

Autoimmune chronic hepatitis types 1, 2, and 3:

Drugs and toxins:

Alpha-methyldopa, Amiodarone, Isoniazid, Methotrexate and Vitamin A.

Genetic metabolic disease:

A1-Antitrypsin deficiency, Amino acid disorders (e.g., tyrosinemia), Bile acid disorders, Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases), lipid disorders (e.g., abetalipoproteinemia). Porphyria, Urea cycle defects (e.g., ornithine carbamoyltransferase deficiency) Wilson's disease.

Idiopathic/miscellaneous:

Granulomatous liver disease (e.g., sarcoidosis), Idiopathic portal fibrosis Indian childhood cirrhosis, Polycystic liver disease.

Infection:

Brucellosis, congenital or tertiary syphilis, echinococcosis, schistosomiasis.

Vascular abnormalities:

Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis, Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease).

Veno-occlusive disease

(Friedman and Schiano, 2004 and Crawford, 2005).

Clinical Presentation:

Cirrhosis often is a silent disease, with most patients remaining asymptomatic until decompensation occurs. Physicians should inquire about risk factors that predispose patients to cirrhosis. The risk factors include those for hepatitis B and C transmission (e.g., birthplace in endemic areas, sexual history exposure risk, intranasal or intravenous drug use, body piercing or tattooing, accidental contamination with blood or body fluids), as well as transfusion history and personal or family history of autoimmune or hepatic diseases ***(Friedman and Schiano, 2004).***

A- Compensated Cirrhosis:

The disease may be discovered at a routine examination or laboratory screening, or at operation undertaken for any other condition. The patient may have mild pyrexia, spider naevi, palmar

erythema, unexplained epistaxis or edema of the ankles. Vague indigestion and flatulent dyspepsia may be early features in alcoholic cirrhosis. Constitutional symptoms such as weakness, fatigue, anorexia, weight loss and low grade fever may occur ***(Friedman and Schiano, 2004 and Diehl, 2004).***

B- Decompensated Cirrhosis:

The patient may be presented by ascites, jaundice or gastrointestinal haemorrhage. Weakness, muscle wasting and weight loss may occur. Continuous mild fever is often due to Gram negative bacteraemia or hepatic cell necrosis. Purpura, spontaneous bruising and/or epistaxis may occur ***(Chung and Podolsky, 2005).***

C- Complications of Cirrhosis:

Patients may present with complications such as:

- Variceal hemorrhage
- Spontaneous bacterial peritonitis (SBP)
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Hepatic encephalopathy
- Hepatocellular carcinoma

(Schepke et al., 2004 and Blei, 2007).

Diagnosis of Cirrhosis:

Laboratory Evaluation:

No serologic test can diagnose cirrhosis accurately. The term liver function tests is a misnomer because the assays in most standard liver panels do not reflect the function of the liver correctly ***(Yee and Lidofsky, 2002).*** When a liver abnormality is suspected or identified, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time test should be performed ***(Dufour et al., 2000a).***

A prospective study showed a strong correlation between liver function test results elevated to greater than twice the upper limit of normal for at least six months and underlying liver disease proved by liver biopsy ***(Skelly et al., 2001).***

Common tests in standard liver panels include the serum enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and g-glutamyltransferase; total, direct, and indirect serum bilirubin; and serum albumin. The ALT is thought to be the most cost-effective screening test for identifying metabolic or drug-induced hepatic injury, but like other liver function tests, it is of limited use in predicting degree of inflammation and of no use in estimating severity of fibrosis ***(Dufour et al., 2000b).***

Additional serologic studies should be pursued to evaluate for various etiologies of cirrhosis. If clinical suspicion for liver disease is high, then further serologic work-up is warranted within six months ***(Dufour et al., 2000b).***

If a patient has a persistently increased ALT level, viral hepatitis serologies should be assayed. If these are negative, the remaining serologic work-up should include an antinuclear antibodies test or anti-smooth muscle antibody test, or both, to evaluate for autoimmune hepatitis; and a fasting transferrin saturation level or unsaturated iron-binding capacity and ferritin level to evaluate for hereditary hemochromatosis ***(Harrison and Bacon, 2005).***

In patients younger than 40 years in whom Wilson's disease is suspected, serum ceruloplasmin and copper levels should be measured, ***(Neimark et al., 2004)*** but screening all patients with chronic hepatic injury for Wilson's disease is not indicated ***(Dufour et al., 2000b).***

Primary biliary cirrhosis or primary sclerosing cholangitis should be suspected in patients with chronic cholestasis. Testing for a1-antitrypsin (A1AT) deficiency may be of benefit in patients with chronic hepatic injury and no other apparent cause. Although the role of A1AT deficiency in liver disease in adults is not clearly defined, testing is especially important in neonates with evidence of hepatic injury ***(Dufour et al., 2000b).***

Radiographic Studies:

Although various radiographic studies may suggest the presence of cirrhosis, no test is considered a diagnostic standard. The major use of radiographic studies is to detect ascites, hepatosplenomegaly, hepatic or portal vein thromboses, and

hepatocellular carcinoma, all of which strongly suggest cirrhosis ***(Friedman and Schiano, 2004).***

1) Ultrasonography (US):

Ultrasonography is routinely used during the evaluation of cirrhotic patients. It is non-invasive, widely available and provides valuable information ***(Nicolau et al., 2002).***

The following ultrasound findings suggest the presence of liver cirrhosis***:***

a- The cirrhotic liver is more echogenic than the normal liver.

b- In patients with advanced cirrhosis, the liver is more coarse than normal, and the surface is irregular because of the presence of regenerative nodules. Surface nodularity is most easily detected when ascites surrounds the liver and highlights its surface. Even fine surface nodularity is abnormal and strongly suggests the diagnosis of cirrhosis.

c- The number of visible portal or hepatic veins is reduced in cirrhotic livers in proportion to the severity of the disease.

d- Findings of portal hypertension include an increased diameter of the portal vein, the presence of collateral veins and splenomegaly ***(Zwiebel, 2000a).***

2) Doppler US:

It provides useful information about portal hemodynamics and collateral vessels ***(Von Herbay et al., 2000).***

3) Computed Tomography (CT):

Computed tomography is not routinely used in the diagnosis of cirrhosis. Early in cirrhosis, CT scans show heterogeneity of liver parenchyma. With advanced cirrhosis, shrinkage of the liver and widening of the intrahepatic fissures are seen. The hepatic contour is usually nodular due to regenerating nodules. Fibrous septa form between the nodules, contributing to heterogeneity of the hepatic parenchyma. Splenomegaly and ascites may be present. CT can also detect collateral vessels developed in portal hypertension ***(Barutcu et al., 2005).***

4) Magnetic Resonance Imaging (MRI):

In addition to demonstrating morphologic changes in cirrhosis, MRI is also useful for evaluation of vascular structures for patency or tumor invasion. It is more sensitive in detecting mass lesions ***(Numminen et al., 2005).***

Histological Diagnosis:

Despite its invasiveness, complications and contra-indications, liver biopsy remains the gold standard in confirming the diagnosis, grading and assessing the extent of scar formation ***(Gebo et al., 2002).*** Biopsy specimens should be large enough to identify portal tracts and central areas ***(Friedman and Schiano, 2004).***

Prognosis of Liver Cirrhosis:

Multiple studies have attempted to predict the prognosis of patients with cirrhosis based upon clinical and laboratory

information as Child-Pugh-Turcotte classification (Child's score) and the Model for End Stage Liver Disease (MELD score) ***(Sheth et al., 2002).***

Model for End Stage Liver Disease (MELD):

MELD is a prospectively developed and validated scoring system that uses the patient's laboratory values for serum bilirubin, serum creatinine and INR. The MELD score, as currently used by UNOS (United Network for Organ Sharing) is useful to evaluate patient for liver transplantation ***(Kamath et al., 2001).*** The MELD score may also be useful in several other clinical settings such as predicting mortality in patients with alcoholic hepatitis and a variety of chronic liver diseases, and those undergoing TIPS (Trans jagular intrahepatic portosystemic shunt) procedure ***(Heuman et al., 2004).***

Anatomy of the Portal Venous System

The portal vein is formed by the union of superior mesenteric vein and the splenic vein just posterior to the head of pancreas at about the level of the second lumbar vertebra ***(Hegab and Luketic, 2001).*** It extends slightly to the right of the midline for a distance of 5.5-8 cm before entering the liver at porta hepatic ***(Sherlock and Dooley, 2002)*** and then divides into right and left portal branches, which enter the corresponding lobes of the liver ***(Zwiebel, 2000a).***

The superior mesenteric vein is formed by tributaries from the small intestine, right colon and head of the pancreas and irregularly from the stomach via the right gastroepiploic vein. The splenic veins (5- 15 channels) originate at splenic hilum and join near the tail of pancreas with the short gastric vessels to form the main splenic vein, which proceeds in a transverse direction. The left gastroepiploic vein joins the main splenic vein near the spleen. The inferior mesenteric vein, bringing blood from left part of the colon and rectum, usually enters its medial third. Occasionally, however, it enters the junction of superior mesenteric and splenic veins ***(Luketic and Sanyal, 2000).***

Additional contribution to the portal venous blood flow is provided by the left gastric (coronary) vein which drains the lesser gastric curvature and the gastroesophageal junction into the proximal part of portal vein ***(Krige and Beckingham, 2001).***

The portal venous blood (low pressured, low oxygenated, nutrient-rich blood) mixes with blood coming from the hepatic arteries (high pressured, well-oxygenated blood), either in portal venules or in the sinusoids. The blood is collected from the sinusoids by the hepatic veins which drain into the inferior vena cava ***(Boyer and Henderson, 2000).***

Portal Hypertension

Definition of Portal Hypertension:

Portal hypertension (PHT) occurs when portal venous pressure gradient exceeds 12 mmHg, or there is an increase in portal venous pressure more than 5 mmHg greater than the inferior vena caval pressure ***(Luketic and Sanyal, 2000 and Robert et al., 2002).***

Pathophysiology:

Two important factors exist in the pathophysiology of portal hypertension, vascular resistance and blood flow ***(Hegab and Luketic, 2001).***

Increase in vascular resistance:

It was found that the initiating event in the development of portal hypertension is increased resistance of portal outflow ***(Hegab and Luketic, 2001).***

Liver disease is responsible for a decrease in portal vascular radius, producing a dramatic increase in portal vascular resistance. In cirrhosis, the increase occurs at the hepatic microcirculation (sinusoidal portal hypertension). Increased hepatic vascular resistance in cirrhosis is not only a mechanical consequence of the hepatic architectural disorder, but a dynamic component also exists due to the active contraction of myofibroblasts, activated stellate cells, and vascular smooth-muscle cells of the intrahepatic veins.

Endogenous factors and pharmacological agents that modify the dynamic component include those that increase hepatic vascular resistance and those that decrease hepatic vascular resistance. Factors that increase hepatic vascular resistance include endothelin, alpha-adrenergic stimulus, and angiotensin II. Factors that decrease hepatic vascular resistance include nitric oxide, prostacyclin, and vasodilating drugs (eg, organic nitrates, adrenolytics, calcium channel blockers) ***(Carale, 2006).***

Increase in portal blood flow

The second factor that contributes to the pathogenesis of portal hypertension is the increase in blood flow in the portal veins, which is established through splanchnic arteriolar vasodilatation caused by an excessive release of endogenous vasodilators (eg, endothelial, neural, humoral). The increase in portal blood flow aggravates the increase in portal pressure and contributes to why portal hypertension exists despite the formation of an extensive network of portosystemic collaterals that may divert as much as 80% of portal blood flow.

Manifestations of splanchnic vasodilatation include increased cardiac output, arterial hypotension, and hypervolemia. This explains the rationale for treating portal hypertension with a low-sodium diet and diuretics to attenuate the hyperkinetic state ***(Carale, 2006).***