INTRODUCTION

Gastroesophageal varices are a direct consequence of portal hypertension that, in cirrhosis, results from both increased resistance to portal flow and increased portal venous blood inflow. Gastroesophageal varices are present at diagnosis in almost half of patients with cirrhosis ***(Garcia-Tsao and Bosch, 2010).***

Although mortality from a variceal bleeding episode has decreased with improved endoscopic and radiological techniques together with new pharmacologic therapies, a 15–20% mortality means that bleeding from oesophageal varices (OVs) remains of significant clinical importance. Early diagnosis of varices before the first bleed is essential as studies of primary prophylaxis clearly show that the risk of variceal haemorrhage can be reduced by 50% to about 15% for large oesophageal varices ***(Vuach et al., 2015)***.

Current guidelines therefore recommend that all cirrhotic patients should be screened for varices at diagnosis, with follow-up every 2–3 years for patients without varices (depending upon liver disease severity) and 1–2 yearly for patients with small varices, to assess for enlargement of varices and need for prophylactic treatment ***(Tripathi et al., 2015)***.

Uppergastrointestinal endoscopy remains the gold standard for screening, but this test is not without its own

limitations. The current guidelines cause a significant burden and cost to endoscopy units, and necessitate patients having repeated unpleasant procedures even when up to 50% may still not have developed oesophageal varices 10 years after the initial diagnosis ***(Lotfipour et al., 2014)***. If it were possible to predict OVs by non-invasive means, this restricts testing to the population deemed to be at most risk and reduce the number of endoscopies required. Such a screening test should be simple, quick, reproducible and cost-effective.

Von Willebrand factor (VWF) is an adhesive plasma glycoprotein which performs its haemostatic functions through binding to FVIII, to platelets surface glycoproteins, and to constituents of connective tissue. VWF acts as a stabilizer of FVIII in the circulation ***(Peyvandi et al., 2011)***.

VWF-Ag plays a crucial role in primary haemostasis and is an indicator of endothelial activation and development of thrombotic vascular obliteration, which are all discussed as possible mechanisms leading to portal hypertension (PHT) ***(Ferlitsch et al., 2012)***.

VWF-Ag is an established and valuable marker for determining the grade of fibrosis and cirrhosis, for prediction of varices, for PHT and for mortality in patients with cirrhosis ***(La Mura et al., 2011)***.

VWF-Ag was significantly higher in patients with OVs than those without varices and its level was significantly higher in patients with higher grade of OVs. The elevated levels of VWF in cirrhosis may be a consequence of endothelial perturbation, possibly caused by bacterial infection. Another possible mechanism of elevated VWF in cirrhosis is induction of synthesis of VWF in the liver with cirrhosis itself, or reduced liver-mediated clearance resulting from decreased expression or activity of ADAMTS13 (VWF-Ag cleaving protease) which may further increase VWF-Ag levels in patients with cirrhosis with PHG ***(Mahmoud et al., 2015).***

AIM OF THE WORK

To assess the level of plasma VWF-Ag in cirrhotic patients with and without oesophageal varices and to evaluate its role in predicting the presence of OVs.

LIVER CIRRHOSIS

Introduction

Chronic liver disease (CLD) affects more than 29 million people in Europe and over 300 million people worldwide. The main causes of CLD are alcohol abuse, chronic viral hepatitis, and metabolic factors (non-alcoholic fatty liver disease). Over time, extracellular fibrotic tissue develops and accumulates in the liver as a result of chronic injury, progressively leading to fibrous septa that prevent normal oxygenation and blood exchange to the liver parenchyma. This late stage, featuring marked liver anatomical changes, including hepatocyte extinction, micro- and macrovascular remodeling, neoangiogenesis, nodule formation, and development of portosystemic shunts, is termed 'cirrhosis ***(Berzigotti, 2017)***.

Liver cirrhosis represents the final stage of liver fibrosis, the wound healing response to chronic liver injury. Cirrhosis is characterised by distortion of the liver parenchyma associated with fibrous septae and nodule formation as well as alterations in blood flow. The natural course of fibrosis begins with a long-lasting rather asymptomatic period, called 'compensated' phase followed by a rapidly progressive phase, named 'decompensated' cirrhosis characterized by clinical signs of complications of portal hypertension and/or liver function impairment (ie, ascites, variceal bleeding, encephalopathy, jaundice) ***(Pinter et al., 2016)***.

Worsening hepatic fibrosis leads to cirrhosis, which can become decompensated and lead, in turn, to hepatocellular carcinoma. Timely intervention can prevent progression to the next disease stage. In particular, it can prevent hepatocellular carcinoma. Appropriate treatment can bring about the regression of disease from a worse stage to a better one. Even cirrhosis can regress, but hepatocellular carcinoma cannot ***(Wiegand and Berg, 2013)***.

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being the 14th most common cause of death worldwide ***(Tsochatzis et al., 2014)***.

According to global burden of disease (GBD) study in 2013, cirrhosis is among the 10 most common causes of death in different world areas and the 6th cause of death in developed countries. The burden is expected to rise in the forthcoming years due to increasing prevalence of cirrhotic cases related to non-alcoholic steatohepatitis (NASH) and hepatitis C virus (HCV) infection ***(Davis et al., 2010)***.

It leads to 1.03 million deaths per year in the world. The 1-year mortality of liver cirrhosis varies greatly from 1% to 57% according to the complications ***(Peng et al., 2016)***.

Pathogenesis

Fibrosis as a precursor of cirrhosis is a pivotal pathological process in the evolution of all chronic liver diseases to cirrhosis ***(Asrani et al., 2013)***.

Liver fibrosis is in fact a healing response to liver injury and is characterized by excessive deposition of extracellular matrix (ECM) proteins as a result of different chronic liver diseases. Hepatic fibrosis can be regarded as the result of an imbalance between ECM synthesis and degeneration. The balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinase (TIMPs) is crucial for ECM homeostasis ***(Trautwein et al., 2015)***.

Many types of cells, cytokines and miRNAs are involved in the initiation and progression of liver fibrosis and cirrhosis. Activation of hepatic stellate cells (HSCs) is a pivotal event in fibrosis. Defenestration and capillarization of liver sinusoidal endothelial cells are major contributing factors to hepatic dysfunction in liver cirrhosis. Activated Kupffer cells destroy hepatocytes and stimulate the activation of HSCs. Repeated cycles of apoptosis and regeneration of hepatocytes contribute to pathogenesis of cirrhosis. At the molecular level, many cytokines are involved in mediation of signaling pathways that regulate activation of HSCs and fibrogenesis ***(Zhou et al., 2014)***.

Liver myofibroblasts (MF) include a heterogeneous population of highly proliferative cells that accumulate at injury sites and promote ECM accumulation. Myofibroblast pool originates mainly from liver mesenchymal cells, namely HSCs. Although HSCs are the primary source of MFs in liver fibrosis, extrahepatic precursors such as bone marrow derived mesenchymal cells and portal fibroblasts contribute in ECM synthesis ***(Ebrahimi et al., 2016)***.

Etiology

Cirrhosis can arise in consequence of an exogenous/ toxic, infectious, toxic/allergic, immunopathological/ autoimmune, or vascular process or an inborn error of metabolism (Figure 1) ***(Manns et al., 2010)***.

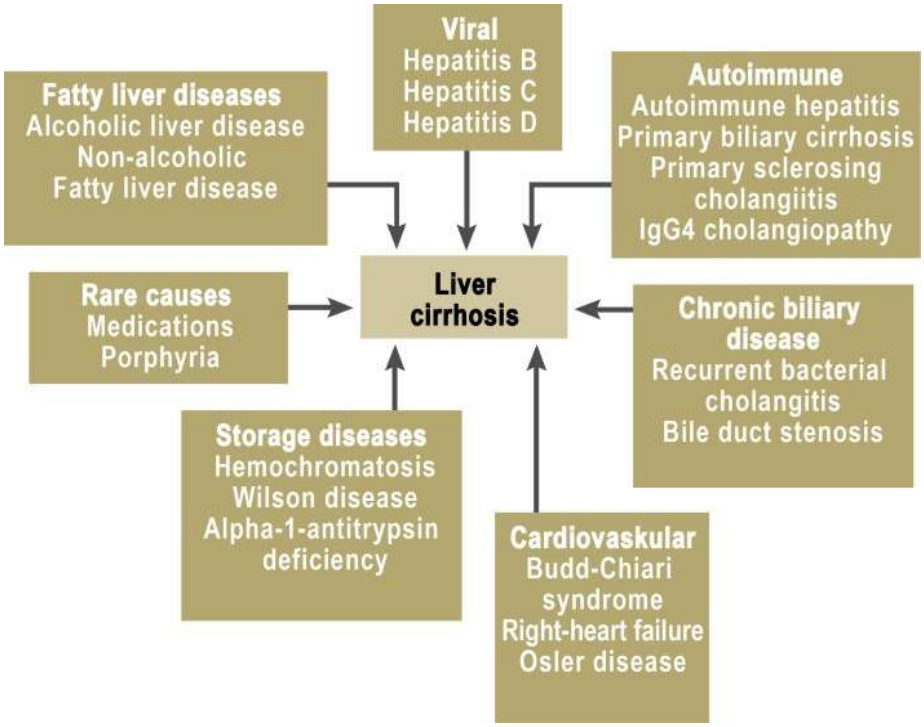

Figure (1): Etioloy of chronic liver disease.

- ***Viral hepatitis***

1-Hepatitis C

Hepatitis C virus (HCV) belongs to the genus Hepacivirus in the family Flaviviridae and is a positive single-stranded RNA virus that is approximately 9.6 kb. The HCV genome encodes three structural (Core, two envelope glycoproteins E1 and E2) and seven non-structural (NS) proteins (NS1 or P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B). As a kind of hepatic tropism virus, HCV mainly replicates in the hepatocyte cytoplasm ***(Li et al., 2018)***.

HCV infects over 170 million humans worldwide, of whom 70%–80% become long-term carriers. Only a minority of infected individuals clear the virus spontaneously, whereas 30–60% of them develop chronic liver disease. Egypt has the highest prevalence of hepatitis C in the world ***(Omar et al., 2017)***.

In 2015, the global prevalence of HCV infection was 1.0%, with the highest prevalence in the Eastern Mediterranean Region (2.3%) followed by the European one (1.5%). The annual mortality due to HCV-related complications is estimated to be approximately 700,000 deaths ***(Kamstra et al., 2016)***.

Seven HCV genotype strains have been identified and classified according to the phylogenetic and sequence analyses of the whole viral genomes. Genotype strains differ at 30%-35% of the nucleotide sites. HCV genotype 4 is the predominant type among chronically infected Egyptian patients ***(Messina et al., 2014)***.

HCV is transmitted most often through exposure to infected blood. Sexual or vertical transmission is rare. The most common route of transmission, before blood donor testing was instituted in 1992, was through blood transfusions. Currently, the most common route of transmission is intravenous drug use, a result of a new epidemic of illicit heroin and prescription narcotic abuse has surfaced among the young ***(Suryaprasad et al., 2014)***.

Other risk factors include intranasal cocaine use, tattoos, piercings, incarceration, hemodialysis and needlesticks in health care workers. Once exposed, 75–80% of individuals will progress to chronic infection. Of these, approximately 10–20% will develop cirrhosis over two to three decades and become at risk for hepatic decompensation and primary liver cancer, hepatocellular carcinoma (HCC). Progression to cirrhosis is accelerated by certain risk factors such as alcohol use, male sex and comorbid diabetes, obesity or fatty liver, or coinfection with human immunodeficiency virus (HIV) or hepatitis B ***(Chen and Morgan, 2006)***.

The diagnosis of acute or chronic HCV infection generally requires testing of serum for both antibody to HCV (anti-HCV) and for HCV RNA. A sensitive quantitative HCV RNA assay is recommended for diagnosis because it also provides information on the level of virus which is helpful in management the differentiation of acute from chronic HCV infection depends on the clinical presentation: namely the presence of symptoms or jaundice, and whether or not there was a prior history of ALT elevation and its duration. After acute exposure, HCV RNA is usually detected in serum before antibody; HCV RNA can be identified as early as 2 weeks following exposure whereas anti-HCV is generally not detectable before 8-12 weeks. These two markers of HCV infection may be present in varying permutations, requiring careful analysis for interpretation (table 1) ***(Ghany et al., 2009)***.

Table (1): Interpretation of HCV Assays

Anti‐HCV	HCV RNA	Interpretation
Positive	Positive	Acute or chronic HCV depending on the clinical context
Positive	Negative	Resolution of HCV; Acute HCV during period of low‐level viremia.
Negative	Positive	Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test
Negative	Negative	Absence of HCV infection

The mass HCV treatment program started administering pegylated interferon and ribavirin between 2007 and 2014 ***(El-Akel et al., 2017)***.

However, the response to pegylated interferon and ribavirin was not satisfactory and was associated with many adverse events ***(El Raziky et al., 2013)***.

The high prevalence of HCV infection in Egypt, which is considered the highest worldwide, prompted the launch of Egypt's pioneering experience against HCV, aiming to eradicate viral hepatitis by 2030. The strategic plan targeted both treatment and prevention of new transmissions, The

introduction of new direct-acting antivirals (DAAs) is a milestone in HCV eradication plan, with sustained virological response (SVR) rate of almost 100% obtained using certain DAA combinations. Preventing new transmissions is a real challenge that requires collaborative efforts to increase population awareness about transmission modes, safe practices, and importance of screening and early diagnosis ***(Omran et al., 2018)***.

Sofosbuvir (SOF) is a milestone of a potent treatment regimen with a favorable safety profile for chronic HCV patients infected with genotype 4. sofosbuvir-based therapies resulted in higher SVR rates compared with the previous standard of care ***(Nagaty et al., 2017)***.

Treatment with SOF (400 mg) plus Daclatasvir (DCV) (60 mg), with or without ribavirin (RBV) (800–1000 mg) for 12 or 24 weeks, was effective and well tolerated in chronic hepatitis C genotype 4 patients. SVR rates were higher for patients with no cirrhosis. Addition of RBV has benefit only in treatment-experienced group receiving 24 weeks ***(ShihaR et al., 2018)***.

2- Hepatits B

Hepatitis B virus (HBV) is a 40–42-nm enveloped virus classified in the Hepadnaviridae family. HBV contains a circular, partially double-stranded DNA genome that is 3.2 kb in length. After a susceptible person is exposed, the virus enters the liver via the bloodstream. The liver is the primary site of HBV replication ***(Chang and Lewin, 2007)***.

HBV is spread predominantly by percutaneous or mucosal exposure to infected blood and other body fluids with numerous forms of human transmission. The sequelae of HBV infection include acute and chronic infection, cirrhosis of the liver and primary liver cancer. The likelihood of progression to chronic infection is inversely related to age at the time of infection ***(Ott et al., 2012)***.

Pregnant mothers with chronic HBV infection can vertically transmit HBV to their infants, and if untreated, chronic HBV infection will develop in 80 to 90% of infants born to mothers who are positive for hepatitis B e antigen (HBeAg) ***(Calvin et al., 2016)***.

HBV is highly infectious, can be transmitted in the absence of visible blood , and remains viable on environmental surfaces for at least seven days ***(Schillie et al., 2018)***.

HBV infection is a considerable global health problem and approximately two billion of the world population have been infected, of which 250 million live with HBV infection ***(Makvandi, 2016)***.

HBV primarily interferes with liver function by replicating in hepatocytes, and it is not directly cytopathic. However, infection with HBV does cause irritation and swelling (inflammation) of the liver. Acute hepatitis B infection does not usually require treatment, and most adults clear the infection spontaneously ***(LeFevre, 2014)***.

Infection of the liver may be either transient (<6 months) or chronic and lifelong, depending on the ability of the host immune response to clear the infection. Chronic infections can cause immune-mediated liver damage progressing to cirrhosis and hepatocellular carcinoma (HCC) ***(Seeger et al., 2015).***

Disease progression to cirrhosis, liver failure, or HCC occurs in up to 40 % of patients with chronic hepatitis B (CHB). Elevated hepatitis B virus (HBV) DNA viral load correlates with increased risk of HCC and cirrhosis ***(Chen et al., 2006)***.

For the past 45 years, studies of HBV, as well as HBV testing, has almost exclusively amounted to detection and quantification of HBsAg. This surface antigen is a clear and inexpensive indicator of chronic HBV infection. However, it does not account for the window period of ~15 days after