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وَقُل رَّبِّ
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Introduction

Hepatopulmonary syndrome (HPS) is defined as the triad of liver disease associated with intrapulmonary vascular dilatation (IPVD) with arterial hypoxemia presented with an alveolar-arterial oxygen tension difference (A-aDO2) more than 15 mmHgor a Partial pressure of oxygen (PaO2) below 80 mmHg ***(Rodrigues-Roisin et al., 2004; Rodrigues-roisin and Krowka 2008).***

HPS is a complication of liver cirrhosis and also reported in some patients with non-cirrhotic Portal Hypertension ***(Ferreira et al., 2009).***

Currently, the only treatment for HPS is Liver Transplantation (LT), two small single-center studies suggested that the presence of HPS is associated with increased mortality in cirrhotic patients evaluated for Liver Transplantation ***(Schenk et al., 2003; Swanson et al., 2005).***

Similarly, survival after Liver Transplantation may be lower in patients with HPS rather than those without HPS***(Krowka, 2005).***

However, resolution of HPS maybe possible after successful Orthotopic Liver Transplantation (OLT) ***(Rodrigues-Roisin et al., 2004).***

The strongest predictor of death was a preoperative partial pressure of oxygen of 50 mmHg or less, and a lung scan with brain uptake of 20% or more***(Arguedas et al., 2003).***

Because of the poor outcome without Liver Transplantation (LT), the diagnosis of the Hepatopulmonary Syndrome associated with a partial pressure of oxygen of less

than 60 mmHg is considered to be an indication for Liver Transplantation, and patients with this syndrome are given a higher priority for transplantation than patients with other disorders ***(Fallon et al., 2006).***

Diagnostic criteria for HPS :

- **Oxygenation defect:** partial pressure of oxygen 80 mmHg or alveolar-arterial oxygen gradient ≥ 15 mmHg while breathing ambient air.
- **Pulmonary vascular dilatation:** positive findings on Contrast Enhanced Echocardiography or abnormal uptake in the brain with radioactive Lung Perfusion Scan.
- **Liver disease:** portal hypertension (most common) with or without cirrhosis.
- **Degree of severity:**
  - ✓ **Mild:** alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen ≥ 80 mmHg.
  - ✓ **Moderate:** alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen ≥ (60-80) mmHg.
  - ✓ **Severe:** alveolar-arterial oxygen gradient ≥15 mmHg, partial pressure of oxygen ≥ (50-60) mmHg.
  - ✓ **Very severe:** alveolar-arterial oxygen gradient ≥15 mmHg, partial pressure of oxygen < 50 mmHg.

(Rodrigues-Roisin et al., 2004; Rodrigues-Roisin & Krowka., 2008)

Aim of the Work

The aim of this study is to assess the prevalence of Hepatopulmonary Syndrome in patients with Chronic Liver Disease.

Chapter (I): Liver Cirrhosis

Definition:

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to Portal Hypertension and end stage liver disease. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in the treatment of its complications, resulting in improved management, quality of life and life expectancy of cirrhotic patients. At present, Liver Transplantation remains the only curative option for a selected group of patients, but pharmacological therapies that can delay progression to decompensated cirrhosis or even reverse cirrhosis are currently being developed ***(Schuppan and Afdhal 2008).***

Epidemiology

The exact prevalence of cirrhosis worldwide is unknown. Cirrhosis prevalence was estimated at 0.15% or 400,000 in the USA ***(NIDDK 1994),*** Where it accounted for more than 25,000 deaths and 373,000 hospital discharges in 1998 ***(U.S National Center for Health Statistics 2005).***

This may be an underestimation according to recognizing the high prevalence of undiagnosed cirrhosis in both NASH and Hepatitis C. Similar numbers have been reported from Europe, and numbers are even higher in most Asian and African countries where chronic viral Hepatitis B or C are frequent. Since compensated cirrhosis often goes undetected for prolonged periods of time, a reasonable estimate is that up to

1% of populations may have histological cirrhosis ***(Schuppan and Afdhal 2008).***

Etiology of liver cirrhosis:

Cirrhosis can arise in consequence of an exogenoustoxic, infectious, toxic allergic, immune pathological (autoimmune), or vascular process or an inborn error of metabolism ***(Wiegand and Berg 2013).***

Cirrhosis and HCC due to chronic Hepatitis C are among the main indications for Liver Transplantation in Western industrialized countries. From 1988 to 2010, viral hepatitis was the underlying cause of liver disease in 39% of Liver Transplantation recipients (Hepatitis B in one-third of cases, and Hepatitis C in two-thirds) ***(European Liver 2012).***

Egypt has the highest prevalence of adult Hepatitis C virus (HCV) infection in the world, affecting an average of 15-25% of the population in rural communities ***(Frank et al., 2000 & Fouad et al., 2012).***

Worldwide, HCV is one of the major causes of Chronic Liver Diseases, which include inflammation, fibrosis and cirrhosis. Furthermore, HCV has been associated with increased morbidity and mortality in Hepatocellular Carcinoma ***(Shaheen and Myers 2007& Sebastiani 2009).***

Causes of Chronic Liver Disease and cirrhosis:

1. Post Viral Hepatitis: HCV, HBV, HDV.
2. Alcoholic Fatty Liver Disease.
3. Non Alcoholic Steatohepatitis (NASH)

4. Chronic biliary disease: recurrent bacterial cholangitis, bile duct stenosis.
5. Cardiac cirrhosis
6. Autoimmune: Auto-immune Hepatitis, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis.
7. Metabolic storage diseases: Haemochromatosis, Wilson disease, Alpha 1 anti-trypsin deficiency, Porphyria.
8. Budd-Chiari syndrome: (hepatic vein obstruction).
9. Drugs and toxins.

(Wiegand and Berg 2013).

Diagnosis:

Cirrhosis is histologically characterized by fibrous septa between the portal fields; it comes in micro and macronodular forms ***(Schuppan and Afdhal 2008 & Berg 2009).*** The condition is diagnosed by its characteristic findings on clinical examination, laboratory tests, and additional studies.

The typical findings in cirrhosis include

- Cutaneous signs of liver disease,
- A firm liver on palpation,
- Certain risk factors such as:
  - Metabolic syndrome,
  - Heavy alcohol consumption,
  - Exposure to hepatotoxic substances,
  - Use of hepatotoxic medications ***(Schuppan and Afdhal 2008 & Berg 2009).***

Table (1): Clinical Features of Cirrhosis:

General Findings [a]	Description	Etiology
Jaundice	Yellow discoloration of skin, cornea and mucous membranes	Compromised hepatocyte excretory function, occurs when serum bilirubin > 2mg/dl
Spider angiomata	Central arteriole with tiny radiating vessels, mainly on trunk and face	Elevated estradiol, decreased estradiol degradation in liver
Nodular liver	Irregular, hard surface on palpation	Fibrosis, irregular regeneration
Splenomegaly	Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Ascites	Proteinaceous fluid in abdominal cavity, clinically detected when ≥ 1.5 L	Portal hypertension
Caput medusa	Prominent veins radiating from umbilicus	Portal hypertension, reopening of the umbilical vein that shunts blood from the portal vein
Cruveilhier-Baumgarten syndrome	Epigastric vascular murmur	Shunts from portal vein to umbilical vein branches, can be present without Caput medusa
Palmar erythema	Erythema sparing the central portion of the palm	Elevated estradiol, decreased estradiol degradation in liver
White nails	Horizontal white bands, proximal white nail plate	Hypoalbuminemia
Hypertrophic osteoarthropathy/Finger clubbing	Painful proliferative osteoarthropathy of long bones	Hypoxemia due to right-to-left shunting, porto-pulmonary hypertension
Dupuytren's contracture	Fibrosis and contraction of the palmar fascia	Enhanced oxidative stress, elevated hypoxanthine

General Findings [a]	Description	Etiology
		(alcohol exposure or diabetes)
Gynecomastia, loss of male hair pattern	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to estrone and estradiol, decreased estradiol degradation in liver
Hypogonadism	Mainly in alcoholic cirrhosis and hemochromatosis	Direct toxic effect of alcohol or iron
Flapping tremor (asterixis)	Asynchronous flapping motions of dorsiflexed hands	Hepatic encephalopathy, disinhibition of motor neurons
Foetor hepaticus	Sweet, pungent smell	Volatile dimethylsulfide, especially in portosystemic shunting and liver failure
Anorexia, fatigue, weight loss, muscle wasting	Occurs in >50% of cirrhotics	Catabolic metabolism by diseased liver, secondary to anorexia
Type 2 diabetes	Occurs in 15-30% of cirrhotics	Disturbed glucose utilization,decreased insulin removal by the liver

(Bircher et al., 1999 & Sherlock et al., 2002 & Schiff et al., 2003 & Groszmann et al., 2005 & Schuppan and Afdhal 2008).

Table (2): Diagnostic algorithm for Chronic Liver Disease:

Screening measures	Step 1: General laboratory testing	Step 2: Specific laboratory testing	Step 3: Molecular and invasive studies
History (identification of risk constellations)	ALT, AST, GGT, AP, bilirubin	Hepatitis serology(HBsAg, anti-HCV)	Ceruloplasmin, copper in 24-hour urine sample, genetic testing for Wilson disease
Physical examination	Complete blood count, platelet count, routine coagulation studies	Autoantibody testing(ANA, SMA, LKM, SLA, p-ANCA, AMA)	HFE mutation: (Hereditary Haemochromatosis)
Serum ALT and GGT	Total protein, albumin, serum electrophoresis	Quantitative immunoglobulins(IgA, IgG, IgM)	A1-antitrypsin genotype (PIZZ)
Ultrasonography	Cholesterol, triglycerides, glucose	Ferritin, transferrin saturation, iron	Liver biopsy, MRCP, ERC (for suspected PSC)

(Wiegand and Berg 2013).

The early signs of cirrhosis in abdominal ultrasonography include inhomogeneity of the hepatic tissue, irregularity of the hepatic surface, or enlargement of the caudate lobe, Portal Hypertension leading to splenomegaly.

In advanced liver disease approaching the stage of cirrhosis, thrombocytopenia is seen, along with impaired hepatic biosynthesis (as shown by, e.g., low concentration of albumin and cholinesterase and an elevation of the International Normalized Ratio [INR] and impairment of the detoxifying function of the liver (as shown by, e.g., elevated bilirubin concentration). The transaminase concentrations are generally in the normal range or only mildly elevated ***(Schuppan and***

Afdhal 2008 & Berg 2009). There is no well-defined threshold value of any laboratory test that can be used to determine when screening for cirrhosis should be performed ***(Wiegand and Berg 2013).***

Esophagogastroduodenoscopy (EGD) can be used to demonstrate esophageal varices, and to assess the risk that they will bleed; it should be performed whenever cirrhosis is initially diagnosed or suspected ***(Schuppan and Afdhal 2008 & Berg 2009)***.

Liver biopsy is unnecessary, or even contraindicated, if the diagnosis of cirrhosis has been clearly established from the clinical findings and imaging studies (e.g., evidence of decompensation, with ascites and impaired hepatic biosynthesis) ***(Wiegand and Berg 2013).***

Liver biopsy is indicated if the etiology of liver disease is unclear, or if its stage cannot be determined from the findings of the tests mentioned above. In cases of suspected cirrhosis, transcutaneous liver biopsy is indicated if the clinical findings leave the diagnosis in doubt or if the biopsy is expected to yield information about the cause of cirrhosis that will affect the choice of treatment ***(Tannapfel et al., 2012).*** To enable the reliable staging of hepatic fibrosis, the punch cylinders used for liver biopsy should be at least 15 mm long, and at least 10 portal fields should be examined per sectional level ***(Schirmacher et al., 2004).***

It should be borne in mind that, once hepatic disease has reached the stage of cirrhosis, histological determination of the original underlying etiology may be difficult or impossible ***(Wiegand and Berg 2013).***

Noninvasive diagnostic evaluation of cirrhosis

A number of laboratory and ultrasound-based methods have been developed recently for the noninvasive diagnostic evaluation of cirrhosis. These noninvasive methods often replace the need for liver biopsy when the only question to be answered is the stage of fibrosis; nonetheless, the information they provide must always be considered in the light of the accompanying clinical findings ***(Castera and Pinzani 2010).***

Laboratory-based methods for estimating the extent of hepatic fibrosis can be divided into those based on routine liver function tests and those based on particular laboratory values that are associated with fibrosis, such as the hyaluronic acid concentration ***(Rosenberg et al., 2004 & Poynard et al., 2007).***

The AST-to-platelet ratio index (APRI) is easily calculated as the quotient of the AST (GOT) and the platelet count and serves as a screening index for advanced fibrosis and cirrhosis ***(Snyder et al., 2006).***

The diagnostic evaluation of cirrhosis with ultrasonography is based on the direct relation between the extent of fibrosis and the ultrasonographically determined degree of liver stiffness. Transient Elastography and the Acoustic Radiation Force Impulse (ARFI) technique are now well-established methods for the staging of fibrosis in various liver diseases ***(Lackner et al., 2006***&***Friedrich-Rust et al., 2008 & Friedrich-Rust et al., 2012& European Liver 2012).*** These two techniques can be performed repeatedly on an outpatient basis, and they can also be combined ***(Castera and Pinzani 2010).***

Techniques for the measurement of liver stiffness and laboratory indices of hepatic fibrosis enable longitudinal assessment of the progression and regression of fibrosis in patients with chronic liver disease. Although ultrasonography can rule cirrhosis in or out in over 90% of cases ***(Friedrich-Rustet al., 2008 & Friedrich-Rust et al., 2012).***Its findings are less than 100% specific because of occasional incorrect measurements and false-positive findings. There may be a difficulty in interpreting values that do not cross the necessary thresholds for ruling advanced fibrosis, or cirrhosis, in or out; in such situations, the temporal course of the variable in question is its clinically relevant feature. It should also be borne in mind that the diagnostic threshold values vary depending on the underlying etiology of liver disease ***(Sebastiani et al., 2011).***

Prognosis and treatment:

The natural history of cirrhosis is dependent on both the etiology and treatment of the underlying cause. Annual rates of decompensation are 4% for HCV, 10% for HBV and the incidence of HCC is between 2-7% per year. Once decompensation occurs, mortality without transplantation is as high as 85% over 5 years ***(Schuppan and Afdhal 2008).***

Numerous studies have attempted to develop a classification system that can both characterize the degree of liver injury and predict the prognosis of patients with cirrhosis based on clinical and laboratory parameters. Due to its low level of complexity and its fairly good predictive value, the Child-Pugh-Turcotte (CPT) classification is widely used. One-

year survival rates for patients with CPT A, B, and C cirrhosis are 100, 80, and 45 percent, respectively ***(Schuppan and Afdhal 2008).***

CPT classification predicts the development of complications, such as variceal hemorrhage and the response of patients to surgical interventions ***(De Franchis and Primignani 1992).***