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A Brief Review on Hepatopulmonary Syndrome

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ABSTRACT

Hepatopulmonary Syndrome is defined as decreased saturation of arterial oxygen due to dilatation of pulmonary vasculature in the presence of portal hypertension or advanced liver disease. In the year 1977, hepatopulmonary syndrome was first proposed based on the clinical findings and autopsy. In the patients with chronic liver disease, pulmonary manifestations like pulmonary vascular dilatation were observed in the autopsies.In the liver disease setting, dyspnea is usually present in the patient. The onset of dyspnea is gradual and aggravates by exertion. Most of the patients are asymptomatic during the early stages. This review article mainly focuses on the epidemiology, pathophysiology, clinical manifestations, diagnosis along with the treatment and management. A multidisplinary approach is required with the involvement of hepatologists, pulmonologists, primary clinicians, addiction medicine specialist, transplant surgeons and clinical pharmacists in the management of HPS.

Introduction

Hepatopulmonary Syndrome (HPS) is defined as decreased saturation of arterial oxygen due to dilatation of pulmonary vasculature in the presence of portal hypertension or advanced liver disease. In the year 1977, hepatopulmonary syndrome was first proposed based on the clinical findings and autopsy. In the patients with chronic liver disease, pulmonary manifestations like pulmonary vascular dilatation were observed in the autopsies. In the liver disease setting, dyspnea is usually present in the patient. The onset of dyspnea is gradual and aggravates by exertion. Most of the patients are asymptomatic during the early stages. Because of cirrhosis or chronic liver disease the association of hepatopulmonary syndrome is most often associated with the portal hypertension. Portal hypertension can cause HPS without any liver disease also. There is no correlation between the severity and presence of HPS with the severity of liver disease [1].

Epidemiology

In the comparison of Hispanics or Blacks with whites, hepatopulmonary syndrome is more usual in whites and is less usual in patients who smoke. The incidence of HPS in patient with cirrhosis ranged from 5% to 32% [2].

Pathophysiology

The imbalance between vasoconstrictors and vasodilators results in dilatation of pulmonary vasculature is considered to be the main cause for HPS. The specific mechanism of vasodilatation is not known and various studies are going to illuminate the specific mechanism. The production of ETB (pulmonary endothelin B) & ET1 (endothelin 1) from liver increases due to stress which causes the stimulation of pulmonary endothelial nitric oxide synthetase (e NOS) in the lungs. The stimulated e NOS increases the production of nitric oxide (potent vasodilator).

In the lungs the accumulation of monocytes and macrophages occurs by the translocation of endotoxemia and intestinal bacteria in the liver disease patients. The inducible nitric oxide synthetase (iNOS) activation takes place by the release of tumor necrosis factor- alpha (TNF- alpha) in the lung vessels by macrophages. There is a raise in production of nitric oxide by the stimulated iNOS. Raised volume of heme oxygenase by the increased nitric oxide (NO) and bacterial accumulation causes the heme degradation and increases the production of carbon monoxide (CO). CO and NO being the potent vasodilators, plays an important role in pulmonary vascular dilatation. Increase in angiogenesis in the lung vasculature by

vascular endothelial growth factor (VEGF) which is activated by TNF alpha, monocytes and also by macrophages. Within the pulmonary vasculature, vasodilation & angiogenesis lead to arteriovenous shunt formation which leads to ventilation perfusion mismatch [3,4].

Hypoxemia and raised alveolar-arterial gradient occurs by ventilation-perfusion match, which is caused by pulmonary vasodilation, impaired diffusion and AV shunts. In the lung bases pulmonary vasodilatation is more distinct elucidating the symptoms like orthodeoxia & platypnoea. Based on the pulmonary vessels location, there are two types of HPS that includes (i) Type I: Dilation of vessels at the precapillary levels near lung gas exchange units. Supplemental oxygen increases PaO2. (ii) Type II: Larger dilation of vessels is responsible for arteriovenous shunts away from lung gas exchange units. Supplemental oxygen is not beneficial [5].

Clinical Manifestations

Pulmonary manifestations are typically the clinical features of HPS. Dyspnea can be gradual in presentation and is the most common manifestation. Platypnoea (dyspnea aggravated by sitting up and improved with lying down), Orthodeoxia (arterial deoxygenation featured in the upright position vs the supine position and accompanies the platypnoea), cyanosis, clubbing and spider nevi were some of the common clinical features [6-8].

Diagnosis

The diagnostic criteria of HPS includes (a)Partial pressure of oxygen (PaO2) <80mmHg or alveolar-arterial oxygen gradient (A-aO2) ≥15mmHg (b)By radioactive lung-perfusion scanning or by positive contrast-enhanced echocardiography, dilatation of pulmonary vasculature is seen (c)Portal hypertension with or without cirrhosis. The severity of HPS depends on PaO2 levels [9].

Table 1: Severity of HPS

Stage	P (A-a)O2mmHg	PaO2mmHg
Mild	≥15	≥80
Moderate	≥15	≥60 - <80
Severe	≥15	≥50 - <60
Very severe	≥15	<50

The differential diagnosis of HPS includes recurrent pulmonary emboli, chronic cardiopulmonary disease, chronic obstructive pulmonary disease, portopulmonary hypertension, pneumonia, hepatic hydrothorax, atelectasis and post pneumonectomy.

Treatment and Management

In severe hypoxemia patients oxygen therapy is suggested. Oxygen therapy is routinely given until a more precised treatment like liver transplantation can be done. Improved quality of life and better exercise tolerance are seen because of reduced hypoxemia and improved oxygenation. In Hepatopulmonary syndrome patients, the established treatment is only the liver transplantation. Improvement in hypoxemia is seen in six to twelve months. Currently, no medical treatment was approved for hepatopulmonary syndrome. Many medical treatments, including pentoxifylline, aspirin, nitric oxide inhibitors, mycophenolate mofetil, garlic, somatostatin, methylene blue and inhaled nitric oxide were tried and none of them showed the efficacy [10].

Conclusion

Patients must be screened for intravenous drug use and alcohol abuse by the primary clinicians. Health care professionals should create awareness regarding overuse of drugs, adverse effects of intravenous drug use and alcohol consumption. Viral hepatitis must be screened in case of high risk patients at least annually. A multidisplinary approach is required with the involvement of hepatologists, pulmonologists, primary clinicians, addiction medicine specialist, transplant surgeons and clinical pharmacists in the management of HPS.

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