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Hepatorenal Syndrome and Hypersplenism

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Abstract

Portal hypertension is characterized by an increased portal pressure gradient which is the difference in pressure between the portal vein and the inferior vena cava and becomes clinically significant when the portal pressure gradient increases to 10 mmHg or above.

Keywords: Portal hypertension; inferior vena cava; intrahepatic vascular resistance

Background

Portal hypertension is a syndrome characterized by an increased Portal Pressure Gradient (PPG) which is the difference in pressure between the portal vein and the inferior vena cava.

Hepatic vasodilators

Nitric oxide: Nitric Oxide (NO), as a powerful endogenous vasodilator, modulates the intrahepatic vascular tone and is produced from the amino acid L-arginine by NO synthases. However, in the cirrhotic liver, NO synthesis is insufficient to compensate for the activation of vasoconstrictor systems frequently associated with cirrhosis. The insufficient hepatic NO production may account for the increased intrahepatic vascular resistance in cirrhosis, thereby worsening portal hypertension [1,2].

Splanchnic vasodilatation

Portal venous blood inflow tends to increase in cirrhosis, particularly in advanced stages of portal hypertension, due to the vasodilatation in the splanchnic organ. The increase in blood flow is one of the key factors which contribute to the pathophysiology of portal hypertension [3]. There are some possible mechanisms which account for the portal hemodynamic abnormalities as neurogenic, humoral, and local mechanisms. Vasodilators in the systemic circulation have been investigated to explain the pathophysiology of portal hypertension. The increased levels of these vasodilators are detected with impaired hepatic function or development of portosystemic collaterals because most of them are metabolized in the liver [4,6].

Endothelins: Endothelins (ETs) are a family of homologous 21 amino acid peptides which include ET-1, ET-2, ET-3, and ET-4. These endothelins exert various biological effects, vasoconstriction, and stimulation of cell proliferation in tissue and one of the major roles of endothelins is to modulate the vascular tone in cirrhosis. Plasma levels of ET-1 and ET-3 are increased in patients with liver cirrhosis and the level is dominant in patients with ascites.

Hepatopulmonary syndrome: Hepatopulmonary Syndrome (HPS) is characterized by the triad of arterial deoxygenation, intrapulmonary vascular dilatation and liver disease. HPS can occur with any degree of liver disease, ranging from well-compensated chronic liver disease without cirrhosis to noncirrhotic portal hypertension and cirrhosis and also been described in patients with acute liver failure.

a) Pathophysiology of HPS: The hallmark of HPS is intrapulmonary vasodilatation markedly at both the pre-capillary and capillary level of the pulmonary circulation especially in the lower lobes. The consequence of the intrapulmonary vasodilatation is arterial deoxygenation by three mechanisms: ventilation/perfusion mismatch, intrapulmonary shunting, and limitation of oxygen diffusion and these three mechanisms contribute to passing of mixed venous blood to the systemic circulation. The etiology of intrapulmonary vascular dilatations is related to an increase in pulmonary NO as a result of expression of both endothelial and inducible NO synthase (eNOS and iNOS, respectively). The link between portal hypertension and increased NO is incompletely understood but seems to be related to an increase in hepatic production of the vasoconstrictor ET-1. A local increase in pro-inflammatory mediators and pulmonary intravascular sequestration of macrophages leading to an increase in iNOS activity and NO production has also been described.

b) Clinical manifestations: The characteristic features in patients with HPS are dyspnoea, digital clubbing, and cyanosis and spider angiomas. Dyspnoea on exertion in case of HPS is probably confounded by physical deconditioning and fatigue, which are very common among patients with cirrhosis. Important manifestations such as platypnoea and orthodeoxia, the increase in dyspnoea or deoxygenation while in the standing position, are classically described in HPS. However, these are not pathognomonic features and actually orthopnoea seems to be a more frequent manifestation in HPS. As in POPH, other physical stigmata of cirrhosis and portal hypertension can be seen in patients with HPS .

c) Diagnosis of HPS: Chest radiographs are usually normal in patients with HPS but can manifest an increased interstitial pattern in the bases, an effect usually caused by arteriovenous shunts in severe HPS. High-resolution computed tomography can identify dilatation of the peripheral pulmonary vessels in the lung bases at early stages of HPS. Measurement of ABGs is the gold standard for identifying arterial deoxygenation and classifying HPS according to the degree of hypoxaemia and PaO2 is the main prognostic determinant for HPS. Contrast-Enhanced TTE (CETTE) has become the most commonly used test for identifying the intravascular vasodilatation of HPS and lung perfusion scanning with Macro-Aggregated Albumin (MAA scan) provides a quantitative assessment of the severity of the intrapulmonary vasodilatation [6].

d) Management of HPS: Currently, there are no effective medical therapies for HPS and liver transplantation is the only definitive therapy with the resultant improvement of arterial deoxygenation and intrapulmonary dilatation occurring almost universally post-transplant. Several studies have addressed the therapeutic potential of compounds affecting the mechanisms involved in the pathogenesis of HPS. Overall, results have not been promising. Supplemental oxygen remains the only proven effective therapy and it should be administered when the PaO2 reaches < 60 mmHg. Transjugular intrahepatic portosystemic shunt should not be considered a therapeutic option for HPS [7].

Several attempts have been made to inhibit the development of HPS by administering nitric oxide, using diets low in L-arginine using methylene blue, which is an inhibitor of guanylate cyclase, aspirin, somatostatin, almitrine, N-acetylcysteine, indomethacin, garlic, mycophenolate mofetil (an inhibitor of angiogenesis and nitric oxide production), pentoxifylline, and using antibiotics to decrease bacterial translocation in the bowel. However, a role for any of these drugs in the long-term treatment of HPS has not been demonstrated.

Portal hypertensive colopathy: Portal Hypertensive Colopathy (PHC) is a frequent complication of chronic liver disease and it may cause lower gastrointestinal bleeding or unidentified chronic anemia in patients with severe portal hypertension.

a) Endoscopic findings: Endoscopic findings in colons of patients with portal hypertension are studied regarding the mucosal and vascular changes. The diagnosed portal hypertensive vascular colopathy are usually classified into four types; solitary and diffuse vascular ectasias, redness in the whole colon and blue rectal vein. Solitary vascular ectasias are found predominantly in the transverse and ascending colon, diffuse vascular ectasias are found predominantly in the right side colon, redness is found in the overall colon and blue vein in the rectum. Mucosal abnormalities in portal hypertension colopathy include edema, erythema, granularity, friability, and vascular lesions, findings that may be confused with colitis.

b) Histopathological study:Dilated tortuous mucosal capillaries with irregular thickening of wall, edema of lamina propria and mild chronic inflammatory infiltrate are the major histopathological changes seen in colonic biopsies of patients with portal hypertension, showing that Portal Hypertension (PHT) produces changes in the colonic mucosa similar to those seen in the mucosa of upper GI tract.

c) Clinical manifestations:Portal hypertensive colopathy may be confused with other causes of colitis and while this disease entity rarely causes bleeding [4]. The lesions of portal hypertensive colopathy are more frequently present in patients with more severe esophageal varices and thrombocytopenia [40]. Child-Pugh class B and C are significantly associated with Portal hypertensive colopathy. Portal hypertensive gastropathy, esophageal varices, ascites and hepatocellular carcinoma are not related to occurrence of portal hypertensive colopathy. Platelet count was significantly decreased in association with portal hypertensive colopathy, but prothrombin time, serum albumin level, total bilirubin level and serum Alanine Transaminase (ALT) level are not usually related to occurrence of portal hypertensive colopathy.

d) Management of PHC:Vasoactive medications, such as octreotide or terlipressin, could be effective in patients with acute bleeding and nonselective β-blockers are recommended as soon as hemodynamic stability is achieved. The use of neodymium:yttrium-aluminum-garnet laser photocoagulation therapy to remove the angioectasias with the probability of remaining free of bleeding for a relatively long period. The portosystemic gradient was reduced after TIPS placement with evidence of reduction in the size and number of colonic lesions. The patient was followed up for 18 months without recurrence of GI bleeding. A better control of lower GI bleeding from numerous angiodysplastic spots in the right colon was achieved after a proximal splenorenal shunt with splenectomy. Colonic varices may be treated with sclerotherapy, surgical ligation and cryosurgery for treatment of anorectal varices. With lower GI bleeding refractory to medical therapy, endoscopic treatment, and TIPS, surgery may be considered [8].

Conclusion

Portal hypertension secondary to hepatic fibrosis and cirrhosis has multisystem effects and multiple complications. The multisystem effects are hepatorenal, portopulmonary hypertension, hepatopulmonary syndrome, portal hypertensive colopathy and others.

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