Hepatopulmonary Syndrome, Severe Cyanosis and Marfanoid Habitus

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**Abstract**

We report the case of a 17-year-old male with Marfanoid habitus who presented with deep cyanosis, haematemesis, dyspnoea and platypnoea. He had oesophageal varices, indicating portal hypertension, with mildly deranged liver function. His arterial blood gas (ABG) revealed hypoxia and orthodeoxia. Contrast-enhanced echocardiography with agitated saline and a 99m Technetium macro-aggregated albumin perfusion lung scan confirmed intrapulmonary shunting. Pulmonary angiogram showed multiple, small diffuse pulmonary arteriovenous fistulae scattered all over the lungs and predominantly in the bases of the lungs. Based on these results and the clinical background a diagnosis of hepatopulmonary syndrome with Marfanoid habitus was made. Patient was treated conservatively as he was not prepared for liver transplantation.

**Introduction**

Hepatopulmonary syndrome (HPS) is defined as a clinical triad of advanced liver disease, arterial deoxygenation and intra pulmonary vascular dilatation. It is a rare complication of liver disease of varied aetiology and has a poor prognosis. The combination of Marfan syndrome and hepatopulmonary syndrome has not been reported in the literature. Many theories have been put forward to throw light over the pathogenesis of HPS. The major clinical manifestations of HPS are cyanosis, clubbing and platypnoea. Arterial hypoxaemia and orthodeoxia are specifically present. A simple noninvasive method to screen the HPS is contrast enhanced 2D echocardiography. No effective medical treatment has been found. Liver transplant seems feasible to reverse (at least partially) this situation in some patients, however it is associated with increased post-operative morbidity and mortality.

**Case Report**

A 17 year old male presented with history of haematemesis (6-7 episodes) and melaena with bluish discolouration of hands and tongue since 10 years. He had breathing difficulty on exertion (NYHA class-II) and platypnoea since 3 years. He had no known cardiac or pulmonary disease. On physical examination, the patient was thin built and tall (height = 180 cm). His arm span was 186 cm. He had a high arch palate and flat plantar arches with positive wrist sign and thumb sign (Figure 1). He had a temperature of 99.4°F, pulse of 82/min, blood pressure of 130/80 mm Hg and respiratory rate of 24/min. The extremities revealed grade 3 pan digital clubbing and cyanosis. He had mild oedema feet. He had gynaecomastia but other signs of liver failure were absent.

Laboratory tests revealed high haemoglobin (19.5 gm%) and normal WBC count. Liver function test showed mildly elevated bilirubin (112 µmol/ L) and serum alanine aminotransferase [69 U/L]. INR was 1.87. Arterial blood gas (ABG) revealed orthodeoxia (supine PO2- 36%, standing PO2 -27% and with oxygen supplement supine PO2- 65%, and standing PO2- 49%). Viral serological markers were negative. Chest X ray showed reticulonodular pattern on bilateral lower zones. There were oesophageal varices indicating portal hypertension. USG abdomen showed normal liver pattern with mild
splenomegaly. ECG showed normal sinus rhythm. ECHO showed pulmonary artery systolic pressure to be 31 mmHg. Normal sized aorta (30 mm) and normal chamber sizes.

On contrast echocardiography with agitated saline, bubbles appeared in the left atrium and ventricle after 4-5 beats, consistent with an intrapulmonary shunt (Figure 2). Lung perfusion scan suggestive of 70.54% intrapulmonary shunt. Pulmonary angiogram showed multiple, small diffuse pulmonary arteriovenous fistulae scattered all over lungs but predominant at the bases (Figure 3).

Based on these results and the clinical background a diagnosis of Hepatopulmonary syndrome with marfanoid habitus was made. Patient was treated conservatively (with oxygen supplement and propranolol) as he was not prepared for liver transplantation.

**Discussion**

Our patient had all three criteria of HPS 1) chronic liver disease with portal hypertension, 2) pulmonary gas exchange abnormalities, 3) evidence of intra pulmonary shunting. Relationship between cirrhotic liver disease and the lung was first described by ‘Fluckiger’2 in 1884 based on a woman with cirrhosis, cyanosis and clubbed fingers. In 1977, Kennedy and Knudson3 coined the term hepatopulmonary syndrome to describe this entity. Marfan syndrome and hepatopulmonary syndrome association was not found in the literature. This patient had both Marfanoid habitus and features of hepatopulmonary syndrome.

In HPS, vascular abnormalities predominate in the lower lung fields. As gravity induces increased blood flow to the lower lung fields, hypoxaemia is increased when changing from supine to an upright position. Mild hypoxaemia occurs in approximately one third of all patients with chronic liver disease and often is multifactorial,4 because other cardiopulmonary abnormalities (e.g., pleural effusion, ascites) are common in these patients and may coexist with HPS. The special qualities of HPS are platypnoea, defined as dyspnoea induced by the upright position and relieved by recumbency and orthodeoxia, defined as arterial deoxygenation induced by the upright position and improved by recumbency.4 Although these phenomena are not pathognomonic for HPS, they strongly suggest this diagnosis in the setting of liver dysfunction.

The prevalence of HPS in the setting of cirrhosis ranges from 4 to 32%.5 The correlation between the severity of liver disease and incidence of HPS remains controversial.4 However, it was reported that HPS occurs occasionally in non-cirrhotic cases of portal hypertension and could completely reverse after the causative agent is eradicated.4 Patient with HPS may be asymptomatic (only 18% have dyspnoea). Platypnoea is well described but not always present, while orthodeoxia is not unique to HPS, but is highly suggestive of it. Severity of hypoxaemia does not correlate with the severity of underlying liver disease. Clubbing, cyanosis and spider nevi may also be present.

Aetiology of this syndrome remains unknown. Most commonly accepted hypothesis postulates that there are alterations in the synthesis or metabolism of pulmonary vasoactive substances by an impaired liver, leading to functional vasodilatation of the pulmonary vasculature resulting in hypoxaemia.6 To date, however, no particular substances have been implicated in causing this dilatation, but possibilities include prostaglandins, nitric oxide, vasoactive intestinal peptide, calcitonin, glucagon, substance P, and atrial natriuretic factor. Hypoxaemia is postulated
to be due to decreased oxygen diffusion into the dilated vessels along with a shortened intrapulmonary blood transit time. The blood transit time is shortened due to the lower vascular resistance in the intrapulmonary circulation and is associated hyperdynamic circulation characteristic of liver disease. Therefore this is not a true shunt and PaO₂ can be significantly improved by supplemental oxygen.

Finally, HPS patients have been found to have decreased hypoxic pulmonary vascular constriction. Intrapulmonary vascular dilatations have been classified into two types based on pulmonary angiography. The more common type 1 lesion is characterised by diffuse pulmonary vascular dilatation and a good response to 100% oxygen administration, while type 2 lesions are more discrete with localised dilatation and a poor response to oxygen. The imaging techniques used to diagnose intra pulmonary vascular dilatation are perfusion lung scanning and pulmonary angiography. Tc 99 m- labelled macro aggregate albumin scan reveals increased radionucleotide activity over the brain and kidney because the large macro aggregate that are normally trapped in the pulmonary vascular circulation pass through the dilated vessels and reach these organs. However this may also occur with intra cardiac shunt, and therefore this test cannot differentiate between the two. The more preferred specific test to diagnose intra pulmonary shunt is contrast echocardiography (micro bubble study). Agitated saline is administered intravenously and based on the number of cardiac cycles completed before the micro bubbles are seen in the left atrium, the location of shunt can be determined. Typically, 4-6 cycles indicate an intra-pulmonary shunt. While 1 to 3 cycles suggest an intracardiac shunt. Finally, pulmonary angiography is the standard invasive method and can differentiate between type 1 and type 2 lesions. Supplemental oxygen improves hypoxaemia and provides symptomatic relief. Other medical therapies have been disappointing and no therapy has been found to modify the disease. Trials of somatostatin analogue, beta adrenergic blockers, sympathomimetics, steroids, NSAIDs and plasma exchange have failed. Spring coil vascular embolisation is an option available to some patients with type 2 lesions. Most promising therapy for patients with severe HPS is liver transplantation.

Fig. 2: Transthoracic Echocardiographic features of the Hepatopulmonary Syndrome. The contrast enhanced echocardiography in Panels A and B show opacification of the right atrium (RA) and right ventricle (RV) with micro bubbles and delayed opacification of the left atrium (LA) and left ventricle (LV), respectively. These findings are the standard for the diagnosis of the Hepatopulmonary Syndrome.

Fig. 3: Pulmonary angiogram showing multiple pulmonary fistulae
HPS was once considered a contraindication to transplantation but now is considered an indication for liver transplantation. Reversal of the hypoxaemia has been reported to occur after transplantation. However, correction of hypoxaemia is unpredictable and may take many weeks to occur. Retrospective data showed that there is a higher mortality rate in patients with HPS than those without HPS. Unique post-operative complication in patients with HPS include pulmonary hypertension, embolic cerebral haemorrhage and post-operative deterioration in oxygenation. For patients with severe pre-operative hypoxaemia (PaO2 < 50 mmHg) and significant intrapulmonary shunting (TC-99m MAA shunt fraction ≥ 20%), the mortality rate may increase further after liver transplantation.5

Conclusions

Hepatopulmonary syndrome should be included in the differential diagnosis of unexplained hypoxaemia /cyanosis with an evaluation of possible portal hypertension or liver disease even in the absence of other clinical symptoms.

References