

Hepatopulmonary Syndrome: A Rare Complication of Chronic Liver Disease in Children

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Abstract

An 11-year-old boy with congenital hepatic fibrosis presented with cyanosis at the National University Hospital. Echocardiogram revealed a structurally normal heart with good ventricular function. A pulmonary cause of his cyanosis was suggested on macroaggregated albumin scan and selective pulmonary artery angiogram. Arterial hypoxaemia secondary to intrapulmonary arteriovenous shunting in chronic liver cirrhosis can lead to permanent cyanosis. The potential for a complete reversal of this condition after liver transplantation indicates that arterial hypoxaemia, rather than being a contraindication, should be a reason for early liver transplantation.

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Introduction

Children with chronic liver disorders may present with dysfunction of other organ systems. Encephalopathy, gastrointestinal bleeding, failure to thrive and impaired renal function are some such findings in these children.¹ Mild to moderate hypoxaemia is also well described in children with chronic liver disease. The clinical syndrome of hypoxia in association with liver disease has been called the hepatopulmonary syndrome (HPS). It consists of the triad of liver dysfunction, intrapulmonary vascular dilatation and hypoxaemia. This arterial hypoxaemia secondary to intrapulmonary arteriovenous shunting can potentially lead to permanent cyanosis, multiple organ failure and death. The long-term definitive management will be a liver transplant. This article discusses the clinical diagnosis of a patient with HPS, reviews the various investigative procedures and summarises the therapeutic strategies available.

Case Report

An 11-year-old Indonesian boy presented to our hospital for evaluation of a one-year history of progressive cyanosis and exertional dyspnoea. He had been previously diagnosed at five years of age to have congenital hepatic fibrosis. At that time, he presented with haematemesis, which on investigation was secondary to

bleeding oesophageal varices. An open liver biopsy was performed and the diagnosis of hepatic fibrosis was made. The child was subsequently lost to follow up until his current presentation. Physical examination revealed a polycythaemic, centrally cyanosed and peripherally clubbed child. His saturation on room air was 86% and his blood pressure was 110/65 mmHg. The rest of the cardiopulmonary examination was normal. The liver was just palpable below the right costal margin and the spleen felt 2 cm below the left costal margin. Multiple telangiectasia were present over his face and upper chest.

Laboratory investigations revealed a haemoglobin of 16.8 g/dL, and good synthetic function of the liver (serum albumin 40 g/dL, normal coagulation profile). Liver enzymes were mildly deranged. Arterial blood gas measurement on room air confirmed his cyanosis with a PaO₂ of 50.5 mmHg, and was not significantly increased (PaO₂ 68 mmHg) when he inhaled 60% oxygen via face mask.

A chest radiograph demonstrated a heart size that was top normal and some non-specific increased vascular markings, particularly in the mid and lower zones (Fig. 1). There were no structural abnormalities on cardiac echocardiography except for a mildly dilated left atrium. Ventricular contractility was good and the

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Fig. 1. Chest radiograph of patient

estimated right ventricular pressure was acceptable (approximately 30 mmHg). A lung perfusion scan with technetium 99m-labelled, macroaggregated albumin showed a brain/lung shunt index of approximately 22% (Fig. 2). This indicates a significant right to left shunt, which, in the absence of a cardiac cause, must be intrapulmonary.

Cardiac catheterisation and pulmonary angiography demonstrated diffuse fine pulmonary arteriovenous fistulae over both lung fields (Fig. 3). There was hold up of contrast and delayed return over several cardiac cycles from the pulmonary veins into the left atrium. The pulmonary arterial pressure was normal with a mean of 10 mmHg. The cardiac output indexed to the body surface area was calculated at 6 L/min/m², which is increased for a child of his age. These findings are consistent with the presence of some amount of pulmonary arteriovenous shunting.

Discussion

HPS is defined as a triad of liver disease, an increased alveolar-arterial gradient while breathing room air, and evidence of intrapulmonary vascular dilatations.* Other cardiopulmonary abnormalities are common associations in children with liver disease and may coexist in patients with HPS.³ This syndrome has been described

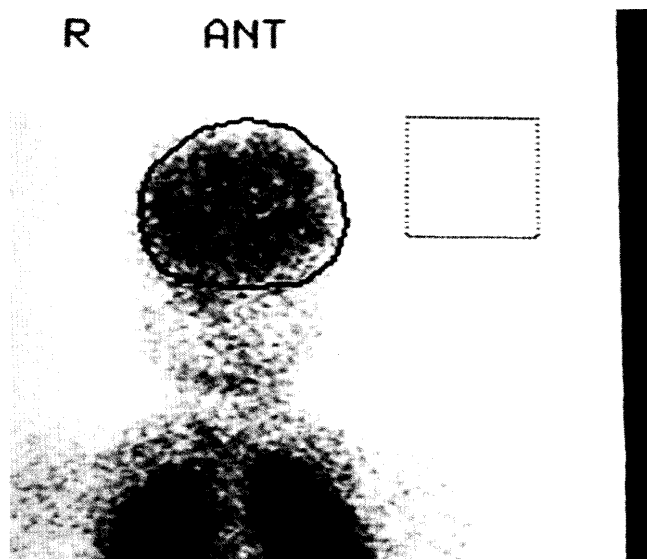


Fig. 2. Macroaggregated albumin scan with uptake of radionuclide over the brain. This indicates transit through the lung via an intrapulmonary shunt, in the absence of an intracardiac cause



Fig. 3. Cardiac catheterisation showing severe diffuse hypervascularity in the arterial phase.

in children as early as in the 1960s.⁴ However, as this is a rare association with chronic liver disease, there have been no large reviews of HPS in childhood until recent reports in the mid-1990s.⁵⁻⁷

Hypoxaemia associated with pulmonary arteriovenous shunting can occur in children with many types of liver disease and at any age.⁷ Although liver cirrhosis was present in most of the patients described, pulmonary arteriovenous shunting has been reported in children with hepatitis,⁸ congenital hepatic fibrosis⁸ and non-cirrhotic portal hypertension.⁹ As with adults, there is no relationship between the occurrence of pulmonary venous shunting and the severity of liver dysfunction.

Empiric evidence from retrospective studies suggests a very strong association between the biliary atresia /

polysplenia syndrome and cyanosis due to intrapulmonary shunts.¹⁰ The risk of developing pulmonary arteriovenous shunts is highest and earliest in children with these features. Further prospective studies are needed to define the prevalence of HPS in childhood although present data suggest that 0.5% of children with portal hypertension, 2% to 4% with cirrhosis and up to 20% to 30% with biliary atresia/polysplenia syndrome will have this complication.⁹

Patients (82%) with HPS present more commonly with hepatic manifestations rather than pulmonary complaints.¹¹ The remainder will present with dyspnoea as the initial symptom and will almost invariably be mildly cyanosed and significantly clubbed at the time of presentation. Other respiratory clues to the diagnosis of HPS are orthodeoxia,¹² (defined as a decrease of PaO₂ of more than 3 mmHg when moving from the supine to standing position) and platypnoea¹³ (dyspnoea induced by the upright position). Spider naevi are also commonly seen and may be a cutaneous marker of intrapulmonary vascular dilatations.^{14,15}

The diagnosis of HPS depends on the documentation of intrapulmonary vascular abnormalities in a patient with typical clinical findings.¹⁶ Although changes are apparent on the chest radiograph, these are usually too non-specific to be of sufficient diagnostic value. Several well-established investigative modalities are currently suggested in the evaluation and diagnosis of HPS.

(1) Contrast-enhanced Echocardiography¹⁷

Intravenous iodocyanine green dye or agitated saline provides a stream of microbubbles 60 to 90 μ in diameter. Under normal circumstances, these microbubbles are filtered by the pulmonary capillary bed and do not appear in the left side of the heart. In the presence of an intrapulmonary or intracardiac shunt, the left chambers will be opacified. In intracardiac shunting, these microbubbles will appear in the left heart within three cardiac cycles after the bubbles are seen in the right heart. In intrapulmonary shunts, the appearance of contrast in the left heart chambers is delayed, occurring only after four to six heart beats.

(2) Lung Perfusion Scan

Albumin macroaggregates exceed 20 μ in size. The normal capillary bed measures between 8 and 15 μ in maximum diameter. Thus a scan showing uptake of radionuclide over the kidneys or brain suggests transit either through an intracardiac or an intrapulmonary shunt. The magnitude of this shunt is estimated by calculating the ratio of systemic to total body activity of the radionuclide, the normal being only 3% to 6% of albumin macroaggregates passing through the pulmonary vasculature.

(3) Pulmonary Arteriography

This procedure allows for direct visualisation of the intrapulmonary vascular dilatations. Although previously considered the gold standard for investigation of the HPS, it is becoming less widely used given the availability of other less invasive methods. It does however have the added benefit of being able to assess the patient for pulmonary hypertension, which is another rare complication of liver disease.¹⁸

Contrast echocardiography is fast becoming the investigative procedure of choice.¹⁹ Not only is it able to exclude intracardiac structural abnormalities as the cause for cyanosis, the microbubble technique is also able to identify patients with intrapulmonary disease who still have normal gas exchange values. At the same time, improvements in lung perfusion techniques have enabled it to remain a favoured diagnostic modality in some centres.²⁰ With these scintigraphic methods, the detection of intrapulmonary shunts is also possible even before hypoxaemia becomes clinically significant.

The effects of therapeutic agents that are theoretically capable of enhancing pulmonary vasoconstriction (e.g. almitrine bimesylate) or of inhibiting vasodilatation (e.g. octreotide,²¹ garlic²² or methylene blue²³) were investigated in small observational studies or case reports. All have shown minimal or no improvement in pulmonary gas exchange.

Other methods using embolisation techniques, surgical decompression or transjugular intrahepatic portosystemic shunts were found to improve oxygenation in single cases,²⁴ but are likely to have a limited role in children for anatomical reasons.

The most rewarding progress being made is with paediatric liver transplantation, where hypoxaemia is no longer a contraindication to liver transplantation. Hobioka et al reported,²⁵ in a review of 9 children who underwent transplant for HPS, that survival was almost 100% if preoperative room air PaO₂ exceeded 60 mmHg. On the other hand, survival was poor if this value was lower. This was also the conclusion reached by Ikeda et al,²⁶ who reported resolution of cirrhosis-related pulmonary shunting in 2 children with liver transplantation.

While many centres presently adhere to the guideline of 60 mmHg, there has been further evidence that other factors may be important in determining outcome, particularly in children. McCloskey et al²⁷ described, possibly the first successful orthotopic liver transplant, in a child with severe hypoxaemia with a preoperative PaO₂ of only 40 mmHg. Barbe et al,⁷ in their review of 26 cases, felt that the post 100% PaO₂ reading may be a better prognostic factor.

Although it is clear that hypoxaemia is not a contrain-

dication for liver transplantation, success is not universal.** The transplant team should bear in mind the importance of adequate post transplant oxygenation and the susceptibility of the liver allograft to hypoxic injury. Since 1995 when the department embarked upon its liver transplantation programme in children, the results have been extremely encouraging. A liver transplant would be the optimal modality of management in this patient at this present stage of his condition. Unfortunately, due to financial and other reasons, the boy returned to Indonesia and was unable to keep up with the suggested treatment and follow-up.

Conclusion

HPS is an uncommon but serious complication of chronic liver disease. Early diagnosis of the condition is important, which can today be easily achieved with the above modalities. As most pharmacological methods are either ineffective or do not address the primary problem, liver transplantation, at this stage, offers the most promising prospect of an effective treatment and potential cure.

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