Hepatopulmonary Syndrome, an Unusual Cause of Hypoxemia

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ABSTRACT

A six-year-old boy presented with cough, cyanosis and clubbing. Investigations revealed hypoxia (PaO$_2$ 53 mmg Hg on room air) which was only partially correctable (PaO$_2$ 73 mm Hg) with 100% oxygen administered through a non re-breathing face mask. Liver function tests showed elevated total bilirubin, and transaminases, liver biopsy confirmed chronic hepatitis and endoscopy showed grade three varices. A contrast enhanced echocardiography (bubble study) revealed pulmonary arterio-venous communication. A diagnosis of hepatopulmonary syndrome was made based on the triad of hypoxemia, liver disease and intrapulmonary vascular communications.

Key words: Hepatopulmonary syndrome; Hypoxia

Liver diseases are rarely considered in the differential diagnosis of a patient presenting with hypoxia, cyanosis and clubbing. Hepatopulmonary syndrome (HPS) and Porto pulmonary hypertension are the two most common underlying causes of hypoxemia in a patient with chronic liver disease or portal hypertension. We describe a case of HPS presenting with hypoxia.

CASE REPORT

A six-year-old boy presented with breathlessness, dry cough, and intermittent epistaxis for one year. Breathlessness had worsened over past 3 months and he developed cyanosis of his fingertips and clubbing. He was treated in various hospitals with multiple courses of inhaled bronchodilators, corticosteroids for suspected bronchial asthma, oral steroids for interstitial lung disease and a course of anti tubercular drugs without improvement. Examination revealed height of 114 cm tall and weight of 15 Kg. He had central cyanosis, grade 2 clubbing and a few spider naevi on the chest and face. There was no icterus. His pulse rate was 142/minute, respiratory rate 52/minute and had nasal flare with chest retractions. The chest was clear on auscultation. Cardiovascular system was normal. Abdominal examination revealed splenomegaly of 2 cms below left costal margin. Liver was not palpable, liver span was 7 cms.

Investigations revealed Hemoglobin of 14.6g%, TLC 5900/mm$^3$, normal differential count, Platelets 98 × 10$^3$/mm$^3$, ESR-60mm in first hour. Blood sugar, serum electrolytes, urea and creatinine were normal. Liver function tests were- bilirubin 3.0 mg/dl (direct fraction 1.4 mg/dl), SGOT 160 IU/L, SGPT 173 IU/L, ALP 383 IU/L, prothrombin time 23 seconds (control 14 seconds). Arterial blood gas analysis revealed hypoxia (PaO$_2$ 53 mmg Hg on room air) which was only partially correctable (paO$_2$ 73 mm Hg) with 100% oxygen inhalation. ABG values on room air and on oxygen are shown in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breathing room air</th>
<th>Breathing Oxygen</th>
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<tbody>
<tr>
<td>pH</td>
<td>7.434</td>
<td>7.40</td>
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<tr>
<td>PO$_2$(mm Hg)</td>
<td>53.4</td>
<td>73</td>
</tr>
<tr>
<td>PCO$_2$(mm Hg)</td>
<td>31.8</td>
<td>39.4</td>
</tr>
<tr>
<td>SPO$_2$(%)</td>
<td>88.6</td>
<td>94.5</td>
</tr>
<tr>
<td>A-a gradient (mm Hg)</td>
<td>50</td>
<td>378</td>
</tr>
</tbody>
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Chest X-ray and HRCT chest were normal. A 2D echocardiography revealed a structurally normal heart. A contrast enhanced echocardiography showed bubbles reaching left atrium and left ventricle after 3 cardiac cycles suggesting an intrapulmonary shunt. CT pulmonary angiography did not show any arterio venous malformation or peripheral pulmonary vascular dilatation.
An underlying liver disease was considered as the cause of pulmonary shunt. Viral markers anti HAV, HBsAg, anti HCV, anti HEV were negative as were autoimmune markers like ANA, ANCA, and anti LKM antibodies. There was no KF ring on slit lamp examination. Serum ceruloplasmin level was 9 mg/dl (normal lab range 17-30 mg/dl) and 24 hr urine copper following a post D-Penicillamine challenge was increased six times (188 micro gram/ day) although basal 24 hour urine copper levels (32 microgram/ day) were within normal range. A liver biopsy showed areas of spotty and piecemeal necrosis, chronic inflammatory infiltrate and fibrosis of portal tract compatible with chronic hepatitis (histological activity index 5/18 and staging 1/6) histochemical stains for HBsAg and HBCAg, and special stains for copper binding protein were negative. Upper gastrointestinal endoscopy revealed grade 3 esophageal varices. A diagnosis of hepatopulmonary syndrome due to an underlying chronic liver disease possibly due to Wilson’s disease was made.

**DISCUSSION**

The hepatopulmonary syndrome (HPS) is a disease entity that is seen in association with liver disease and is one of the many extra hepatic manifestations of liver failure. The triad of liver disease, hypoxemia, and intrapulmonary vascular dilations characterizes HPS.

The diagnosis of hepatopulmonary syndrome in our case was based on: absence of intrinsic cardiopulmonary disease, pulmonary gas exchange abnormalities in form of partial correction of hypoxia with oxygen inhalation, evidence of intrapulmonary shunting as suggested by echocardiography and presence of chronic liver disease as indicated by: splenomegaly, grade 3 esophageal varices, raised transaminases and bilirubin and prolonged prothrombin time. This was further supported by histopathological changes in form of spotty and piecemeal necrosis, chronic inflammatory infiltrate and fibrosis of portal tract chronic with chronic hepatitis (histological activity index 5/18 and staging 1/6). The diagnosis of Wilson’s disease was not confirmed. The basis for presumed diagnosis was: low blood ceruloplasmin, 6 fold increase in copper excretion after challenge with D penicillamin and no alternative diagnosis for chronic liver disease.

We ruled out possibility of congenital pulmonary arteriovenous fistula in our patient by doing a CT angiography. However, pulmonary angiography is an invasive tool and is usually reserved for those patients who have severe hypoxemia and a poor response to 100% inhaled oxygen.

Hepatopulmonary syndrome is an under recognized entity. The estimated prevalence of HPS in children with chronic liver disease is 5-29%. Clinical presentation is variable. No consistent relationship between biochemical indices of hepatic dysfunction or intrapulmonary vascular shunt has been conclusively shown. A case of Hepatopulmonary syndrome has been reported in 6-year old-child with subclinical chronic liver disease secondary to vascular anomaly (Abernethy malformation, type 1) with normal liver function test.

The major cause of hypoxemia in HPS is felt to be due to intrapulmonary vascular abnormalities. HPS primarily affects the precapillary arterioles and capillaries in the lung bases, producing dilation of these vessels. Normally, these vessels measure approximately 8 to 15 micrometer. In the presence of HPS, these vessels may exceed 500 micrometer in diameter. Because of the abnormal dilation of the pulmonary vessels, blood flowing only adjacent to the alveolus becomes appropriately oxygenated. The inability of oxygen to diffuse to the center of these abnormally dilated vessels and couple to hemoglobin contributes to the diffusion –perfusion defect and an apparent right-to-left intrapulmonary shunt.

HPS can occur with a number of underlying liver disease like cryptogenic cirrhosis, chronic active hepatitis, biliary atresia, non cirrhotic portal hypertension, Alpha1 -antitrypsin deficiency (Pi ZZ), Wilson’s disease and tyrosinemia. Dyspnoea is the most common symptom. Platypnoea and orthodeoxia, representing shortness of breath and oxygen desaturation respectively on assuming the sitting position are characteristic clinical features. Additional clinical features include clubbing, cyanosis, and the presence of cutaneous spider nevi. Spider nevi may have special significance in the hepatopulmonary syndrome as they may be a marker of intrapulmonary vascular dilatations.

To date many medical therapies have been tried for HPS, including indomethacin, aspirin, almitrine, somatostatin and garlic but none has been clearly beneficial. The only successful, long-term treatment currently available is liver transplantation. Eighty-five percent or more of patients with HPS who receive liver transplantation experience either significant improvement or complete resolution of hypoxemia. A preoperative arterial oxygen tension (PaO2) of < 50 mm Hg alone or in combination with a macro aggregated albumin shunt fraction> 20% were the strongest predictors of postoperative mortality. In our case, the child was started on oral D-Penicillamine and Propranolol and discharged on home oxygen therapy. The family could not go for liver transplantation due to financial reasons.

**REFERENCES**