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A severe (type II) hepatopulmonary syndrome in a patient with idiopathic portal hypertension and treatment with paroxetine

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ABSTRACT

The hepatopulmonary syndrome has been defined as chronic liver disease accompanied by abnormal pulmonary gas exchange, which might result in arterial deoxygenation, and widespread intrapulmonary vasodilation. Although it has been pointed out that hepatopulmonary syndrome occurs in liver cirrhosis, there are a few studies in the literature reporting noncirrhotic portal hypertension as a cause of hepatopulmonary syndrome. Currently, liver transplantation is the only effective therapy for such patients. On the other hand, there is also a proposal about considering paroxetine, a potent nitric oxide synthase inhibitor, for use in the hepatopulmonary syndrome. We present a patient with severe (type II) hepatopulmonary syndrome caused by idiopathic portal hypertension and discuss the consequences of paroxetine therapy.

KEYWORDS

Hepatopulmonary syndrome, paroxetine

INTRODUCTION

Hepatopulmonary syndrome (HPS) is recognised by progressive pulmonary complications that include severe liver disease and/or portal hypertension, abnormal arterial oxygenation, and presence of intrapulmonary vascular dilatations.[1] There might be severe hypoxaemia with arterial PO_2 <60 mm Hg (8 kPa), dyspnoea, cyanosis, digital clubbing, orthodeoxia and platypnoea in these patients. Its incidence in patients with liver cirrhosis is about 10%,[2] and in the literature this rate is 10 to 20% in patients who are candidates to liver transplantation.[3,4] A few cases of noncirrhotic portal hypertension (NCPH) complicated by HPS have been published.[5,6] Therefore the cirrhosis is not a strict criterion for HPS identification. We present here a patient with a classical presentation of severe HPS, which was caused by idiopathic portal hypertension, and we discuss the effect of paroxetine therapy on this syndrome.

CASE REPORT

An 18-year-old male patient was admitted to our clinic at the beginning of 2004. He had fever, fatigue, and dyspnoea. His symptoms were intermittent and alleviated after antibiotic therapy, which he had been receiving since the previous year. In many attacks, cyanosis, palpitations and intolerance to exercise also occurred. He had also been suffering from a depressed mood on a daily basis for a period of three months. He had been hospitalised because of Brucella disease one year earlier. There was no history of pica. Physical examination revealed cachexia, pale conjunctiva, frank cyanosis of the tongue, lips and the distal part of extremities, finger clubbing, splenomegaly, and spider nevus on his shoulder. Laboratory findings revealed the following: haemoglobin 6.4 mmol/l, haematocrit 0.31, white blood count 1.9 x 10^9/l, platelet count 83 x 10^9/l, and erythrocyte sedimentation rate 75 mm/h. Serum aspartate aminotransferase was 0.89 U/l, alanine aminotransferase 0.71 U/l, lactic dehydrogenase 4.04 U/l, alkaline phosphatase 4.6 U/l, γ-glutamyl-

transpeptidase 1.66 U/l, total bilirubin 11.9 μmol/l, iron concentration 7.09 μmol/l, total iron binding capacity 75.6 μmol/l, transferrin saturation rate 9%, albumin 39 g/l, and globulin 32 g/l. Reticulocytes count, seruloplasmin, thyroid hormones, cortisol, and corticotropin levels were normal. Haemoglobin and protein electrophoresis were also normal. Serum markers for hepatotropic and nonhepatotropic viruses, ANA, anti-LKM-1, anti-SLA, pANCA, and AMA-M_2 were all negative. Prothrombin time was 15 seconds, activated partial thromboplastin time, protein S and antithrombin III were normal, but protein C level was low (36.6%). Analysis of the sweat chloride value was normal in duplicate. In DNA analysis, gene mutation for cystic fibrosis (ΔF 508 and ΔTA 1677) was absent. Respiratory function test was compatible with moderate restriction. The alveolar-arterial oxygen gradient (A-aPO_2) was 68 mmHg (9 kPa) in upright position. Partial arterial oxygen tension (PaO_2) was 53 mmHg (7 kPa) in supine position and 45 mmHg (6 kPa) in sitting position (orthodeoxy). Response to 100% inspired oxygen was 54 mmHg (7.2 kPa). Arterial blood gas values in upright position revealed pH 7.47, PCO_2 29 mmHg (3.8 kPa), SaO_2 81%, and HCO_3 23 mmol/l. The carbon monoxide diffusing capacity (DL_{CO}) of the lung was 42.4 (% predicted). Electrocardiogram and posteroanterior lung X-ray and thorax high resonance computerised tomography were normal. Macroaggregated albumin (^{99m}Tc-MAA) scintigraphy revealed heterogeneous radioactivity distribution in the lung fields. There was obvious tracer uptake over the brain, spleen and bilateral kidneys, with shunt fraction of 20%. Standard echocardiogram revealed normal findings. Contrast echocardiography showed microbubbles after four heart beats (late opacification) in left heart chambers with 4+ degree of opacification (*figures 1A* and *1B*). He did not tolerate transoesophageal echocardiography. Cardiac output was calculated and found to be 8 l/min on cardiac catheterisation by the Fick method. The results of this procedure are summarised in *table 1*. The value of hepatic venous pressure gradient (HVPG) was 6 mmHg. The endoscopy showed grade 2 to 3 oesophageal varices and portal gastropathy. Doppler ultrasonography of abdominal-portal system revealed a normal-sized liver, normal parenchymal echogenity, dilated portal vein (*figure 2*), mild splenomegaly and splenic venous dilatation (*figure 3*). There was no image of cavernous transformation of the portal vein. Liver biopsy showed noncirrhotic liver parenchyma with normal architecture, dilated sinusoids and portal space, degenerated hepatocytes, periportal-portal inflammation (*figure 4*), porto-portal bridging fibrosis and sclerosis (*figure 5*). In the light of all these parameters, the diagnosis of HPS caused by NCPH was made. He also fulfilled all the criteria for major depression, according to the psychological consultation. We gave him paroxetine (Seroxate® tb) 20 mg a day orally for six months because

Figure 1A *Microbubbles in right heart chambers in contrast echocardiogram*

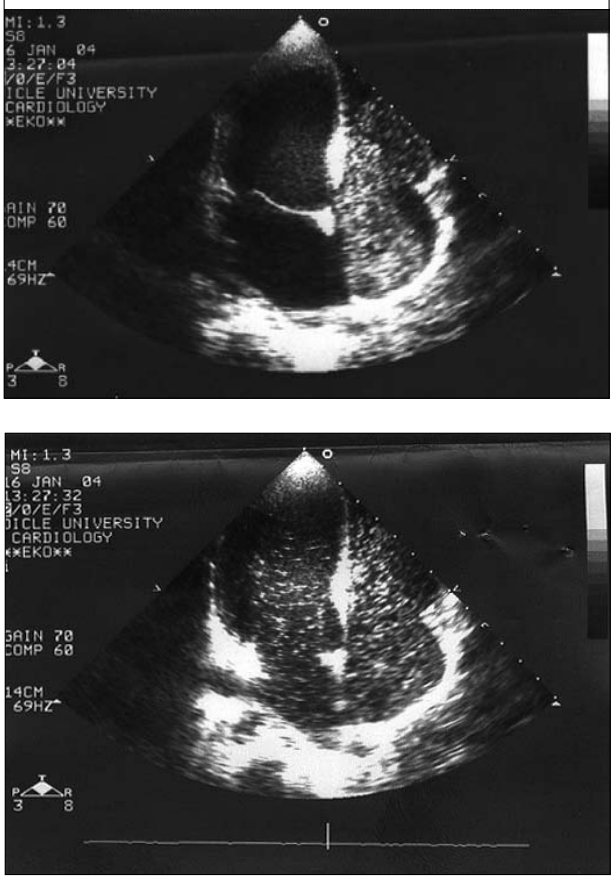


Table 1 *Parameters obtained from cardiac catheterisation*

Angiography	Pressures (mmHg)	SAO_2 (%)	PAO_2 (mmHg)
Pulmonary artery	20/10	67	40
Right ventricle	20/0	69	40
Right atrium	5 (mean)	70	40
Aorta	100/70	87	56

Figure 2 *Liver ultrasonogram: dilated portal vein without cavernous transformation*

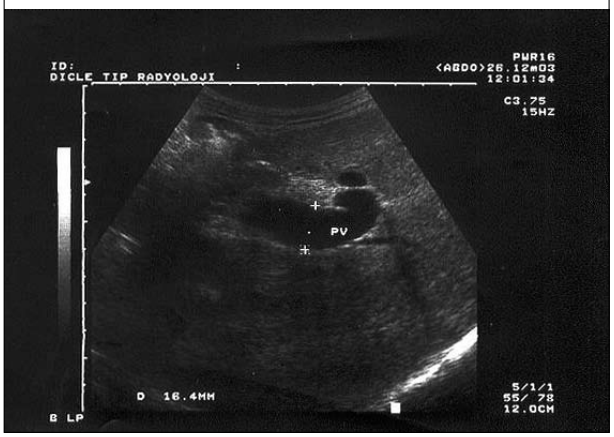


Figure 3 *Spleen ultrasonogram: splenomegaly with dilated splenic vein*

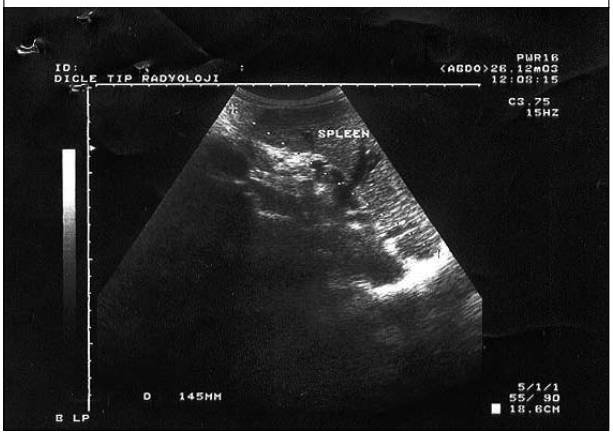


Figure 4 *Liver biopsy shows portal-periportal inflammation, and hepatocellular degeneration (HE x 200)*

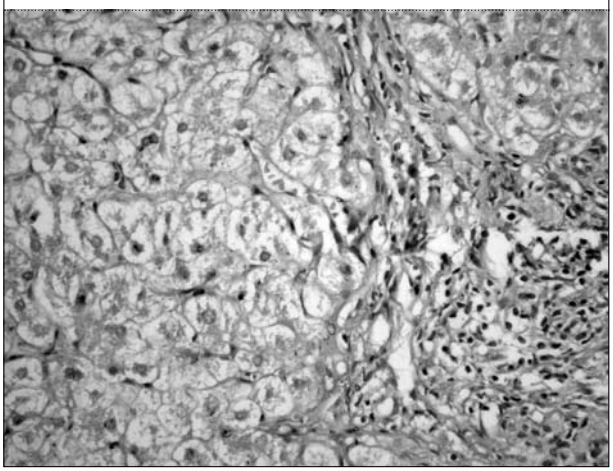
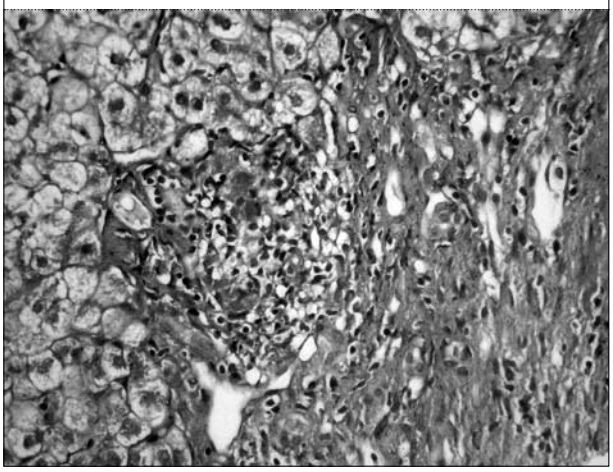


Figure 5 *Liver biopsy shows periportal fibrosis with Masson's trichrome staining (x 200)*



of its antidepressant effect and the possibility of NO-synthetase inhibition resulting in a decrease in intrapulmonary shunting. The blood gas parameters at the end of treatment are summarised in *table 2*.

Table 2 *Results associated with before and after paroxetine treatment*

		Results	
		Before	**After**
A-aPO_2 gradient		68	75
100% O_2 test (PaO_2-mmHg)		54	61
PaO_2 (mmHg)	Supine	53	40
	Upright	45	35
SaO_2 (%)	Supine	83	65
	Upright	81	63

DISCUSSION

In the definition of hepatopulmonary syndrome, the presence of cirrhosis is still frequently one the criteria[7-9] but it is obvious that HPS is also seen in patients with noncirrhotic portal hypertension.[10] Recently, in a study performed by Kaymakoglu *et al.*, it was pointed out that HPS might occur in both liver cirrhosis and noncirrhotic portal hypertension and that portal hypertension is the predominant pathogenic factor related to HPS.[6] However, pathogenesis of HPS is still obscure. This is likely to be a manifestation of decreased hepatic clearance or increased hepatic production of circulating cytokines and other vascular growth mediators such as endothelins, nitric oxide (NO), and prostaglandins. Increased sensitivity to these mediators is another theory. The major role was attributable to the potent vasodilating mediator nitric oxide. Besides, endothelin-1 increases inducible NO syntheses and plays an important part in intrapulmonary vasodilatation in HPS.[11] As we mentioned above, for NCPH, severe liver dysfunction is not mandatory for intrapulmonary vasodilatation. The other reasons for an impaired oxygenation because of shunting are pleural spider naevi, intrapulmonary A-V shunts and portopulmonary venous anastomoses.

Arterial hypoxaemia is described as PaO_2 <70 mmHg (9.3 kPa) in blood gas analysis; <60 mmHg (8 kPa) reflects severe hypoxaemia. Hypoxia is believed to result from an inability of oxygen to diffuse to the centre of dilated vessels up to tenfold in diameter in HPS.[12] Low level of PaO_2 does not reflect gas exchange disturbance in liver disease alone, because of hyperventilation and hyperdynamic circulation in cirrhosis. Therefore, measuring the A-aPO_2 gradient is better, and a level >20 mmHg (2.6 kPa) is pathological and important in HPS diagnosis. It was 68 mmHg (9 kPa) in our patient. On the other hand, 100% oxygen inspiring test (breathing 100% oxygen through a mouthpiece and wearing nose clips for 20 minutes in the sitting position) is another supplement. The test of supplementation with 100% oxygen distinguishes HPS type I from type II. In type I, there is a close to normal response

to the administration of oxygen (PaO_2 >400 mmHg (53.3 kPa)), but in type II, an inadequate response to this regimen.[4] In the study carried out by Kaymakoglu *et al.*, there were three patients with HPS in the NCPH group and all of them had levels >150 mmHg (20 kPa). This level was 54 mmHg (7.2 kPa) in our patient, which is compatible with type II HPS and reflects a severe intrapulmonary shunt. The cases reported to have HPS caused by NCPH in the literature were not as severe as our patient. Contrast echocardiography is one of the best modalities confirming intrapulmonary dilatations.[7] Positive echocardiogram for HPS was defined by the detection of delayed visualisation of microbubbles in the left heart chambers after three to six contractions. If microbubbles are visualised after one to two contractions, this reflects intracardiac right-to-left shunting. There was a result compatible with the intrapulmonary shunt in our patient with a higher degree of opacification (4+), compared with the cases in the study of Kaymakoglu *et al.*, and this result may also support the severity of shunting. Pulmonary angiography is the most invasive procedure in diagnosis of HPS and shows emboli and/or other causes of hypoxemia. There are two patterns in angiographic examination of HPS patients.[12] In type I, there is a normal vascular structure, spongiform, spotted image, and patients respond to 100% oxygen supplementation test. In type II, there are vascular dilatations such as arteriovenous communications and a poor response to treatment by medications or transplantation.

As we previously stated, our patient had severe HPS. The portal hypertension was of unknown origin. There was no evidence of liver cirrhosis. There was a prehepatic intrasinusiodal portal hypertension pattern in data obtained from hepatic venous catheterisation in our patient wedged hepatic venous pressure (WHVP) and HVPG normal. No portal or splenic venous thrombosis was found in the imaging studies. Schistosomiasis was also excluded by microscopic findings. There was no history of medication or herbal abuse in our patient. We could not detect any pattern compatible with partial nodular transformation in imaging studies. Serum markers for early primary biliary cirrhosis and primary sclerosing cholangitis were negative. Furthermore, there were no signs of myeloproliferative disease or sarcoidosis. Finally, there was no evidence of congenital hepatic fibrosis cholangitis.

Idiopathic portal hypertension (IPH) is also called noncirrhotic portal fibrosis or hepatoportal sclerosis, and known as a conditon in which liver function is preserved. However, patients with IPH who develop hepatic failure late after the illness have been reported.[13] The pathogenesis of the portal hypertension in these patients is unknown. Some investigators believe that the principal abnormality is in the portal venules. Microthrombi in the portal venules or sclerosis of the portal veins may be seen. High portal venous flow and increased intrahepatic resistance are also present. Pathologically, the following findings were present: alterations in small vessels, regarded as the initial lesion, and changes in liver architecture consisting of fibrosis and/or nodule formation, regarded as secondary. However, in obstructive portal venopathy, the suspected initial lesion is not always found in a biopsy specimen.[14] When an obvious venular obstruction is not seen, many endogen factors consist of cytokines, and activated coagulation factors may cause stellate cell activation followed by perisinusoidal fibrosis. There are prothrombotic disorders in approximately 50% of these patients and this phenomenon may play a crucial role in the pathogenesis of IPH.[15] HVPG is normal or moderately elevated in patients with IPH. In the light of these data we conclude that our patient has IPH with protein C deficiency, with preserved liver function and exclusion of liver cirrhosis.

The struggle to find the underlying disease is the essential approach in the treatment of HPS. The strategy to remove circulating vasodilators by for instance allium sativum, indomethacin, and almitrine bismesylate was found to have marginal effects. Embolotherapy can be tried in patients with type II HPS who have widespread intrapulmonary vascular dilatations.[16] Transjugular intrahepatic portosystemic shunting may improve levels of PaO_2 and may be feasible, especially to gain time for liver transplantation. Severe hypoxaemia used to be considered a contraindication to liver transplantation, but liver transplantation is still the single proven treatment option to cure HPS nowadays.[17]

As suggested in the literature[18] we treated our patient with paroxetine, a selective serotonin reuptake inhibitor with nitric oxide synthase blocking properties. We gave this drug for six months because of HPS and major depression. His depressive mood responded to the treatment, but we saw no improvement in blood gas parameters (summarised in *table 2*), Tc-99-m MAA scintigram, contrast echocardiogram or in clinical status. Paroxetine was given to the patients with HPS caused by cirrhosis in the mentioned study. The unknown pathogenesis of portal hypertension in noncirrhotic patients makes it difficult for as to know how to treat them. In the light of our findings, we presume that NO may play a minor role in HPS caused by IPH. On the other hand, lack of response to NO-reducing agents may be explained by progression of the liver disease. We could not perform the second liver biopsy because of a low platelet count (43000/μl). There is an increasing trend towards extrahepatic portal vein thrombosis in patients with this disease, and anticoagulant therapy is proposed to maintain portal vein patency.[15] Our patient had high-grade oesophageal varices that were prone to bleed and thrombocytopenia, so we did not consider giving him anticoagulant therapy. Finally

our patient, who has a poor prognosis, is now in the liver transplantation programme because there is no other effective treatment available in our country.

CONCLUSIONS

This case supports the literature about HPS caused by noncirrhotic portal hypertension. The findings in our patient were rather severe when compared with cases of HPS caused by NCPH reported in the literature. Treatment with paroxetine did not alter the course of the disease. There is thus a need for a more extensive cohort of noncirrhotic portal hypertensive patients with these features, and studies on many other treatment options to overcome the controversial points.

NOTE

A color version of this case report can be found on our website www.njmonline.nl.

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