ORIGINAL ARTICLE

FREQUENCY AND PREDICTORS OF HEPATOPULMONARY SYNDROME IN CHRONIC LIVER DISEASE PATIENTS

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ABSTRACT

Introduction: Hepatopulmonary syndrome is not very uncommon among chronic liver disease patients in clinical practice.It is associated with shorter survival and poor liver function in cirrhotics. Although there are a large number of CLD patients in India, the exact frequency of HPS is not known & it needs evaluation.

Aims: To estimate the frequency of hepatopulmonary syndrome among Indian patients with chronic liver disease, study the correlation between HPS and the severity of liver disease and assess the factors predictive for diagnosis of HPS.

Methodology: A cross sectional study on total fifty patients (34 males, mean age 44.4 ± 7.3years) with chronic liver disease was conducted to diagnose the presence of hepatopulmonary syndrome. Patients were subjected to clinical examination, laboratory investigations, measurement of arterial blood gas and transthoracic contrast enhanced echocardiography. The severity of liver disease was assessed by Child-Pugh score.The diagnostic criteria for HPS were presence of intrapulmonary vascular dilatation(IPVD) documented by contrast enhanced echocardiography and alveolar arterial oxygen gradient of more than 15 mm Hg.

Results:. Nine of fifty patients (18%) with chronic liver diseas were found to have contrast echocardiographic evidence of intrapulmonary vasodilatation. Hepatopulmonary syndrome was observed in seven (14%) patients.We did not find any significant correlation between presence of HPS with severity of liver disease according to the Child-Pugh score. Features like dyspnoea, orthopnea, cyanosis, clubbing, platypnoea and orthodeoxia were significantly more common in the HPS group.

Conclusions: The frequency of HPS among the studied group of Indian patients with chronic liver disease was 14%. Though there was no significant correlation between presence of HPS with severity of liver disease according to the Child-Pugh score ; but presence of cyanosis, clubbing, dyspnoea and platypnoea–orthodeoxia are suggestive indicators of HPS.

Keywords: Hepatopulmonary Syndrome, Chronic Liver Disease, Dyspnoea, Orthopnea, Cyanosis, Clubbing

INTRODUCTION

Hepatopulmonary syndrome is a very important complication in patients with cirrhosis and portal hypertension due to alteration in pulmonary vasculature by different mechanisms. It is characterized by the triad of chronic liver disease, namely cirrhosis and/or portal hypertension;features of arterial deoxygenation and presence of intrapulmonary vascular dilatations (IPVD).[1,2,3] This syndrome is frequently underdiagnosed,mostly in early stages,due to the fact that most of the affected patients are either asymptomatic or present with vague complaints of shortness of breath and easy fatiguability. [4] HPS is reported to occur in 11% to 32% of the patients with chronic liver disease (CLD), mainly cirrhotic patients.[5,6,7,8]

Clinical features like dyspnea, cyanosis, platypnea, spider nevi and clubbing are more frequent in patients with HPS when compared to those without HPS [3,7] It should also be mentioned that HPS is associated with more severe CLD, assessed either by the Child-Pugh (CP) score or by the Model for End-Stage Liver Disease (MELD) score, in some but not all the studies.[4,5,9,10] The natural course of HPS was generally progressive and it was associated with shortened survival. No effective medical therapies are available for HPS, although liver transplantation reverses the syndrome in most patients.[11,12]

The objective of the present study was to determine the prevalence of HPS in a sample of Indian patients with chronic liver disease and to compare clinical, and laboratory characteristics in patients with and without HPS.

METHODOLOGY

Total 50 patients of established chronic liver disease who were admitted or under outpatient department follow up of department of General Medicine, Medical College & Hospital, Kolkata from February 2014 to January 2015 were included in our study. All of them underwent bubble contrast echocardiography for detection of IPVD. Arterial blood gas analysis was done in the patients who were contrast positive, to measure alveolar-arterial oxygen gradient & degree of hypoxemia.The patients with positive contrast echocardiography along with widened alveolar-arterial oxygen gradient (A-a Gradient>15 mm of Hg) was diagnosed as hepatopulmonary syndrome. Patients with pre existing cardiac or pulmonary disease, those having abnormal chest X ray or chronic smokers were excluded from our study. Diagnosis of CLD was based on history, clinical examination, blood biochemistry,ultrasonography of abdomen, upper GI endoscopy & liver histology, whenever a liver biopsy specimen was available.The etiology of CLD was evaluated in all the patients.Severity of CLD was determined by using Child-Pugh score. Written informed consent was obtained from the patients and the study protocol was approved by Institutional Ethics committee for human research, Medical College,Kolkata. Patients were followed for one year after their diagnosis.

Procedures:

Contrast Echocrardiography- All patients underwent a contrast enhanced transthoracic echocardiogram (CE),using Vivid 7 Dimension machine equipped with 3 S transducers. Apical four-chamber view was used for the simultaneous visualization of the atria and ventricles. Peripheral venous access was obtained through the left antecubital fossa of each patient. The procedure was performed by injecting agitated 0.9% saline into patient's left hand cubital vein. Left and right sides of the heart were evaluated by echocardiography. Normally, the injected microbubbles travel from the right ventricle to the lungs, where they are absorbed in the pulmonary circulation and do not reach the left ventricle. Those with intracardiac shunts, microbubbles reach the left ventricle early (within one to three cardiac cycles after injection). In patients with intrapulmonary shunting(IPVD in hepatopulmonary syndrome), microbubbles reach the left ventricle in a delayed fashion (three to six cardiac cycles after injection).Two exams were performed on each patient and each subsequent injection was initiated after complete disappearance of the microbubbles from all cavities. The results were analyzed by two examiners.

Arterial blood gases analysis-All contrast positive patients undergone arterial blood gas analysis. Arterial blood gas samples were obtained by percutaneous radial artery puncture with the subject in a seated position breathing room air, and were analysed with a standard blood gas analyser (OPTI CCA-TS Blood gas & Electrolyte analyser using OPTI Cassettes). AaDO2 was calculated using the alveolar gas equation.Abnormal AaO2 and hypoxemia were considered in patients with AaO2 levels of more than 15 mm Hg and PO2 of less than 80 mm Hg. Arterial blood gas samples were obtained in recumbent position and after being upright for 20 min to determine the presence of orthodeoxia which means PaO2 fall by 5% in the upright position as compared to the value in recumbancy.

Criteria for diagnosis of HPS - HPS was diagnosed in the presence of abnormal AaO2 and of pulmonary vascular dilatation assessed by CE echocardiography. The patients with positive contrast echocardiography along with widened alveolar-arterial oxygen gradient (A-a Gradient>15 mm of Hg) was diagnosed as hepatopulmonary syndrome.Hepatopulmonary Syndrome severity was determined based on oxygenation abnormalities. Mild, moderate, severe and very severe Hepatopulmonary Syndrome was considered in the presence of PaO2 equal or more than 80 mm Hg; PaO2 less than 80 mm Hg and equal or more than 60 mm Hg; PaO2 less than 60 mm Hg and equal or more than 50 mm Hg and PaO2 less than 50 mm Hg, respectively.[8] **Statistical Analysis-** Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes. Continuous variables are expressed as Mean ± Standard Deviation and compared across the 2 groups using Mann-Whitney U test since the data does not follow normal distribution The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

RESULTS

Total 50 patients of established chronic liver disease (34 Males)were included in our study. 15 other patients of CLD can not be included as a part of the study due to presence of other cardiopulmonary disease in some of them and patient refusal in the rest (as per exclusion criteria). In our study population, we found that most of the cases of CLD were alcoholic(44%) in etiology. Chronic hepatitis B and hepatitis C were responsible for 14% and 8% of cases respectively. Cryptogenic group comprise of about 30% of cases. Others(4%) include one case of Wilson's disease and one auto immune hepatitis. Of the total study population, most patients was in Child Class B (48%) and C (32%).

Table 1: Laboratory features of the patients according to the presence of HPS

Variable	HPS		
	NEGATIVE	POSITIVE	
	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value
AGE	43.98 ± 7.38	47 ± 6.61	0.280
SPO2(%)	97.07 ± 1.08	93.43 ± 2.88	0.001
FBS(mg/dl)	88.3 ± 18.1	93.57 ± 13.97	0.149
T.BIL(mg/dl)	3.2 ± 2.5	5.31 ± 4.67	0.154
D.BIL(mg/dl)	1.69 ± 1.6	2.96 ± 3.99	0.287
ALT	53.07 ± 48.13	38.57 ± 9.68	0.502
AST	73.35 ± 63.57	76 ± 67.84	0.685
ALBUMIN	2.96 ± 0.43	2.89 ± 0.46	0.933
GLOBULIN	4.02 ± 0.5	4.14 ± 0.83	0.877
Hb(gm%)	10.16 ± 1.62	8.54 ± 1.38	0.017
PT(TEST)	16.08 ± 2.23	17.74 ± 4.35	0.493
INR	1.39 ± 0.23	1.47 ± 0.35	0.823
CHILD SCORE	8.33 ± 1.74	9.57 ± 1.62	0.108

Table 2: Clinical features of the patients according to the presence of HPS

FEATURES	HPS		
	Positive (n=7) (%)	Negative (n=43) (%)	p Value
H/O Jaundice	5 (71)	24 (56)	0.438
H/O Weight Loss	6 (86)	32 (74)	0.516
H/O UGI Bleeding	3 (43)	11 (26)	0.345
Dyspnoea	6 (86)	16 (37)	0.017
Platypnoea	3 (43)	3 (7)	0.007
Cyanosis	1 (14)	0 (0)	0.012
Clubbing	4 (57)	5 (12)	0.004
Spider Naevi	4 (57)	11 (26)	0.091
Orthodeoxia	2 (29)	0 (0)	<0.001
Hepatomegaly	2 (29)	18 (42)	0.506
Spleenomegaly	7 (100)	30 (70)	0.091
Ascites	6 (86)	31 (72)	0.446
Varix In UGI Endoscopy	7 (100)	34 (79)	0.181

To determine the frequency of hepatopulmonary syndrome all the 50 patients of CLD undergone transthorasic contrast echocardiography with use of irrigated normal saline.Total 9 patients out of them showed positive results. so 18% of the study population showed presence of IPVD (intra pulmonary vascular dilatation) in the form of positive contrast echocardiography. Arterial blood gas analysis was done in these 9 patients to calculate (A-a) gradient. According to the cut off used (A- a gradient >15mm of Hg), 7 patients showed gas exchange abnormalities in the form of widened (A-a) gradient. So, the frequency of Hepatopulmonary syndrome in our study population was 14%.

Among the 7 diagnosed patient of hepatopulmonary syndrome, total 6 patients were included in alcoholic & cryptogenic group (3 each). Only one patient had chronic hepatitis B. Out of the 7 cases 4 patients were in Child Class C, 3 were in Child Class B & none were in Child Class A. Hepatopulmonary Syndrome severity was determined based on oxygenation abnormalities. Mild, moderate, severe and very severe Hepatopulmonary Syndrome was considered in the presence of PaO2 equal or more than 80 mm Hg; PaO2 less than 80 mm Hg and equal or more than 60 mm Hg; PaO2 less than 60 mm Hg and equal or more than 50 mm Hg and PaO2 less than 50 mm Hg, respectively. Among the 7 patients, 4 had moderate, 3 had mild & none had severe or very severe disease based on oxygenation.

Clinical and laboratory features of the patients according to the presence of HPS are depicted in Table 1 & Table 2. There was no statistically significant difference in the features like h/o jaundice, h/o weight loss or h/o upper GI bleeding in the HPS patients with the non-HPS group. Dyspnoea was present in 6 out of 7 patients of HPS (86%), whereas it was present in only 37% of the non-HPS patients.Platypnoea,the presence of dyspnoea on assuming upright posture, was present in 3 out of 7 patients of HPE(43%) whereas it was present in 3 out of 43 patients (7%) in non-HPS group. Both presence of dyspnoea and platypnoea was significantly higher in HPS patients in comparison with the non-HPS patients. Cyanosis & orthodeoxia was present in only 1 & 2 patients respectively in the HPS group whereas they were not present even in a single patient in non-HPS group. Clubbing was present in 4 out of 7 patients of HPS(57%) whereas it was present in 5 non-HPS patients (12%). On the otherhand, spider naevi was present in 57% of HPS patients & 26% of non-HPS patients.There was significanctly higher occurance of cyanosis, clubbing, orthodeoxia among the HPS patients in comparison to the non-HPS group. There was no significant difference of hepatomegaly, splenomegaly, ascites & varix in endoscopy in the HPS group & non-HPS group.

It was found that there was significant difference in SpO2, Hemoglobin (gram%) in the HPS patients in comparison to the non-HPS group.There was no significant difference in other parameters including the mean Child Score among these two groups.

DISCUSSION

In our study, we found that, the frequency of contrast positivity (IPVD) was 18% & the frequency of hepatopulmonary syndrome was 14%. All of them had mild to moderate HPS. Etiologically three of them had alcoholic liver disease, three had cryptogenic CLD & only one had Chronic Hepatitis B.Four of the HPS patients belong to Child C & rest three to Child B class. The frequency of HPS in our study is within the reported range as described in literature, where it is reported to be 11-32%.[4,5,6,8,9,13] The frequency of hepatopulmonary syndrome varies widely in different studies depending upon the different methods and diagnostic criteria used for its diagnosis. There is significant difference in cut off values as diagnostic criteria, thresholds used for the definition of de-oxygenation, types of contrasts used & different diameters of microbubbles used as a contrast in echocardiography.

A study by Abrams GA et al. with 40 cirrhosis patients showed presence of intrapulmonary vaodilatations (IPVD) by contrast echocardiography in 15 patients(38%).[5] Out of them 7 patients had gas exchange abnormalities.So,HPS in this study group was 17.5% among cirrhotic patients. Another study conducted by Gupta D et al. was done with 54 patients of cirrhosis.[6] HPS was diagnosed in a patient with positive CEE, in the presence of hypoxia ($PaO_2 < 70$ mm Hg) and/or elevated alveolar arterial oxygen gradient of > 20 mm Hg in the absence of any underlying cardiopulmonary disease. Ten of 54 patients (18.5%) with cirrhosis were positive on CEE and Six of the 10 patients positive with cirrhosis for CEE had associated hypoxia. Thus, HPS was found in 11.1% in patients with cirrhosis in this study. A study by Ferreira PP et al. included 125 patients of chronic liver disease who underwent evaluation for HPS.[9] The presence of pulmonary vascular dilation and HPS was observed in 21 (17%) and 19 (15%) of the patients, respectively. Based on oxygenation parameters, eight (6%) patients had mild HPS, nine (7%) had moderate HPS, two (2%) had severe HPS and none had very severe HPS. All patients with HPS were further submitted to 99mTcMAA for shunting quantification. Twelve out of the 19 (63%) patients with HPS had shunting by 99mTcMAA and all were graded as mild by scintigraphy. Our study found no correlation of HPS with the severity of Chronic Liver Disease assessed by Child Pugh score(mean Child score of 8.33 ± 1.74 in HPS patients vs 9.57 ± 1.62 in non-HPS). Though HPS occurs in advanced CLD patients, but this is not unexpected.As most of the patients included in our study was decompensated & naturally they had a high Child score. Most of the studies fails to correlate the association of HPS with the severity of liver disease as assessed by Child score.[4,5] A study by Ferreira et al. found significant relationship of HPS with severity of liver disease as assessed by MELD score but not by Child score.[9] Another study by Schenk et al. found association of HPS and severity of liver disease assessed by both MELD score & Child score.[10] The significant relationship of HPS with severity of liver disease found in this study may be due to the fact that they had investigated HPS in compensated & ambulatory CLD patients.

Among the different clinical features, the presence of dyspnoea, platypnoea (dyspnoea worsened by an erect position and improved by a supine position), orthodeoxia (exacerbation of hypoxia and hypoxemia in an upright position), cyanosis & clubbing was significantly higher in HPS patients in comparison with the non-HPS subjects in our study. We found that most of the HPS patients was dyspnic(6 of 7 patients). Though platypnoea was significantly higher in HPS group, we found that three of the non-HPS patients also had complaints of platypnoea. Platypnoea without HPS in them can be explained by mechanical causes. Cyanosis was present in only one HPS patient & Orthodeoxia in only two patients of HPS, but they were present in none of the non-HPS group. Clubbing was present in 57% of HPS patients in contrast to its presence only in 12% of the patients without HPS. The pathogenesis of digital clubbing in patients of HPS is not completely understood. One hypothesis is based on the fact that megakaryocytes and platelet aggregates are retained principally by the pulmonary capillaries. In patients with a right-to-left-shunts, those megakaryocytes reach the digital capillaries, there releasing platelet derived growth factor (PDGF). PDGF is responsible for increased capillary permeability and proliferation of fibroblasts that causes clubbing. Though presence of spider naevi was higher in HPS group (57% in HPS vs. 26% in non-HPS), its presence was not significant.

Our results were in accordance to the previous reports, where they found higher incidence of dyspnoea, platypnoea & orthodeoxia.[14] Presence of platypnoea & orthodeoxia in those patients was attributed to the predominance of vasodilatation in the lung bases and the increased "shunting" through these regions when upright leading to hypoxemia. Different studies also showed higher prevalence of cyanosis, clubbing & spider naevi in HPS.[2,7,14] The similar types of results except spider naevi was observed in our study. Though presence of spider naevi is regarded as a very important cuteneous finding in HPS, but some researchers failed to establish the finding. A study by Deibert P et al. showed no significant correlation between spider angioma & hepatopulmonary syndrome.[15] The absence of significant relationship between the presence

of Spider naevi & HPS in our study may be due to the fact that in presence of dark complexion, spider angioma may be missed; they can also be present in CLD patients without HPS & relatively smaller sample size of our study. Measurement of oxygen saturation by pulse oximetry is a very useful non-invasive method for initial suspicion of HPS in chronic liver disease patients. Some authors are of opinion that, SpO2 measured by pulse oxymeter, if found to be lower then they should undergo arterial blood gas analysis & contrast echocardiography to diagnose HPS.[16] In our study we found significant difference in SpO2 (%) values in HPS & non-HPS patients(Mean SpO2 of 93.43 ± 2.88 in HPS patients vs. 97.07 ± 1.08 in non-HPS patients).

Our study did not find any significant difference in Liver function tests (Total bilirubin, direct bilirubin, liver enzymes, prothombin time, INR) abnormalities in patients of hepatopulmonary syndrome.Similar types of findings were also found in previous studies.[17] Another interesting finding found in our study was significantly lower hemoglobin (gram%) in HPS patients in comparison to those without HPS (Mean hemoglobin of 8.54 ± 1.38 in HPS vs. 10.16 ± 1.62 in non-HPS). Previous studies do not show any significant correlation of hemoglobin with HPS. This finding in our study may be due to the fact that, HPS usually occurs in advanced & decompensated CLD. They are anemic due to the liver disease itself, upper gastrointestinal bleeding in the form of hematemesis & melaena, presence of other nutrient deficiencies etc.

In our study, seven cases of hepatopulmonary syndrome was prescribed to take garlic daily. Out of the seven patients, 4 patients expired within one year of diagnosis.Two of them survived & one lost follow up.This is in accordance to previous studies which show that most patients develop progressive intrapulmonary vasodilatation and worsening gas exchange over time and that spontaneous improvement is rare. Mortality rate is significantly higher and quality of life is significantly compromised in patients with HPS compared with those without HPS.[18,19]

Therefore, 14 % of patients in our study had hepatopulmonary syndrome.Though these results are based on a smaller subset of CLD patients,but the results suggest that HPS in India is not very uncommon in CLD patients.HPS is mostly underdignosed or undiagnosed initially as the patients are either asymptomatic or presents with vague complaints like shortness of breath & easy fatiguability. Further Indian studies may be needed on this topic so that this pulmonary complication of CLD can be diagnosed early.

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