ORIGINAL ARTICLE

INDICATORS OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH PORTAL HYPERTENSION. ITS VARIOUS AETIOLOGIES, CLINICAL PRESENTATIONS AND OUTCOME

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Background: Hepatopulmonary syndrome is severe pulmonary vascular complication of chronic liver disease requiring liver transplant. This study was conducted to evaluate different indicators of HPS in patients with portal hypertension, its varied aetiologies, clinical features & outcome. **Methods:** Hospital based descriptive study, 203 patients were enrolled, divided in to 2 groups positive and negative on the basis of presence or absence of HPS as per diagnostic criteria. **Results:** It included 203 patients with portal Hypertension of varied aetiologies. Age range was 8.76±3.69 years. 54.7% were male & 45.3% female. Commonest diagnosis for portal hypertension was portal vein thrombosis in 48 (23.6%) while Least common was biliary atresia seen in 6 (3%) of cases. Fifteen patients were included in Positive group and 188 in negative group. Clinical & laboratory parameters in order of frequency in positive group were hypoxia & cyanosis in 100% & 93.3% followed by dyspnoea & grade 4 clubbing in 86.6% patients (p<0.001). Child scoring was also done in all patients. In negative group 7 (3.7%) had dyspnoea, I (0.53%) had grade 4 clubbing while none showed evidence of hypoxia or cyanosis (p<0.001). Three patients underwent successful liver transplant. One patient of biliary atresia & another of CHF expired. **Conclusion:** In All children with CLD and/or PHT with unexplained dyspnoea, cyanosis and grade 4 clubbing, HPS should be suspected. It is an indication for early LT even in absence of liver failure.

Keywords: Hepatopulmonary syndrome (HPS); Arterial oxygen tension (PaO2); Alveolar-arterial oxygen gradient (A-a) O2 gradient; Contrast-enhanced echocardiography (CEE); technetium-99m Macro aggregated Albumin (99 mTc-MAA), Liver Transplant (LT)

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INTRODUCTION

Hepatopulmonary syndrome is a gas exchange disorder, defined as a triad of arterial hypoxemia, cirrhosis or portal hypertension, and evidence of intrapulmonary vascular dilatation.[1] Fluckiger in 1884 described first female patient of Hepatopulmonary Syndrome (HPS) with symptoms including cirrhosis, cyanosis, and digital clubbing. Knudson in 1977 described HPS as a disease.[2] It could be due to an imbalance between the production and clearance from liver of vasoactive vasodilators and cytokines, prompting microvascular dilatation within the pulmonary arterial circulation. Antagonists for same vasodilators and cytokines could be potential future treatment targets.

Diminished liver functions and inflammation recruiting inflammatory cells which accumulate in the lungs by bacterial translocation, endotoxemia leading to increased circulating TNF-alpha, causing pulmonary angiogenesis.[3] Microvascular dilatation & pulmonary angiogenesis leads to ventilation-perfusion mismatching, oxygen diffusion limitation, bringing about anatomical and functional shunt physiology causing arterial hypoxaemia. Compared with an intracardiac shunt defect, oxygen supplementation corrects the hypoxemia due to V/Q mismatch and diffusion defect.[4]

Prevalence of Hepatopulmonary Syndrome (HPS) varies from 4–47% in adults.[5] In Paediatric age group it observed in 9–20% of patients of biliary atresia & 0.5% with Portal vein thrombosis.[6] Noli *et al*[7] detected HPS in 8% of 301 children with cirrhosis or severe PHT. But exact prevalence in children is unknown. We conducted this study to delineate different aetiologies of hepatopulmonary syndrome in paediatric patients with portal hypertension, diverse clinical manifestation and outcome. Most useful screening test is pulse oximetry, but the gold standard is arterial blood gas analysis portraying Arterial- alveolar (A-a) gradient and P02. Abnormal P (A-a) O2 gradient should prompt performing either, a contrast-enhanced echocardiography (CEE) or a perfusion lung scan using technetium-99m Macro aggregated Albumin (99 mTc-MAA).[8] We suggest screening of all patients with portal hypertension for presence of hepatopulmonary syndrome as early intervention like liver transplant in these patients may reduce morbidity and mortality.[9]

MATERIAL AND METHODS

We screened 203 patients under 18 years of both gender with portal hypertension secondary to varied

aetiologies, for presence of hypoxia. These cases were enrolled and followed up in liver unit of The Children's Hospital, Lahore. Study precluded over 2 years, i.e., from 01-01-16 to 31-12-17. All patients underwent portal Doppler USG and surveillance upper GI endoscopy to confirm presence of portal hypertension. The cut-off portal vein diameter chosen for diagnosing portal hypertension was upper limit of normal, i.e., 15 mm or 1.5 cm by Doppler USG. All possible causes for portal hypertension Including prehepatic (Portal Vein Thrombosis), hepatic (Chronic liver disease), Post hepatic (Congenital hepatic fibrosis, Budd Chairi Syndrome, hepato-caval syndrome) were included in the study. Diagnosis of chronic liver disease due to different causes had already been made in all patients by pertinent clinical, biochemical & histo pathological tests. Patients were labelled as cryptogenic CLD where extensive work up failed to identify aetiology. We used the Child–Pugh score for determining liver disease severity. Pulse oximetry was done in all patients for identifying hypoxaemia. Duration of liver disease was also noted on a preformed *proforma*. We used universal diagnostic criteria for HPS in our patients, i.e., the presence of portal hypertension / CLD with evidence of hypoxaemia [in room-air pulse oximetry <96% or arterial oxygen tension (PaO2) of <70 mmHg on arterial blood gas and any intrapulmonary shunting observed on CEE or 99 mTc-MAA Patients who were found to have pulse oximetry SpO2 <96%, were included in positive and those who were above 96% were taken as negative group. The one with hypoxia positive group patient sunder went Contrast Enhanced Echo to determine the presence of intrapulmonary shunting. After determining the normal cardiac anatomy, 10 mL of the agitated normal saline solution was rapidly injected into the patient's venous cannula and echocardiographic images were digitally recorded for analysis. The time at which contrast appeared in the right & then in left ventricle & the number of cardiac cycles between these times were recorded. An abnormal CEE scan was defined by the appearance of contrast in the left ventricle after 3 cardiac cycles after its appearance in the right ventricle. Appearance after 20 cardiac cycles was defined as normal. We calculated Alveolar-arterial (A-a) gradient in 9 of our positive group patients & 99 mTc-MAA was performed in only 4 of our patients. Financial constraint and non-availability in our hospital limited its application in all patients. A 99 mTc-MAA perfusion scan was performed with the child in the upright or standing position, 0.05 m Ci/kg 99mTc-MAA was injected into a peripheral venous cannula. After 20 minutes, quantitative whole-body imaging was performed with a dual-head camera. Quantitative evaluation of relative uptake was determined using regions of interest drawn over the brain, kidney, soft tissues, and lungs. The shunt index (expressed as a ratio of the uptake in the lungs to the uptake in the total body minus kidney activity) was measured. A positive scan was defined as a shunt fraction greater than 4%.

Clinical features in terms of (dyspnoea, cyanosis, grade 4 clubbing) of 15 patients of positive group were compared with 188 cases of negative group. Xray chest and renal function tests were done in all patients to exclude any concomitant lung or renal pathology. So, Primary cardiopulmonary diseases were excluded from the study. Collected data was analysed using SPSS version 20. Frequency was calculated for qualitative variable including gender, diagnosis etc. Mean and SD were calculated for quantitative variable like age, duration of liver disease. Chi square test was applied as test of significance for any qualitative variable, *p* value ($p<0.05$) was taken as significant.

RESULTS

The study was carried out in 203 patients of either sex, different racial and economic backgrounds, on the basis of consecutive non-probability sampling. Age range was 8.76±3.69 years. The number of male and female patients was 111 (54.7%) and 92 (45.3%), respectively (Table-3). Most common underlying diagnosis for development of portal hypertension was portal vein thrombosis in 48 (23.6%) followed by cryptogenic liver disease in 46 (22.7%). Hepatocaval syndrome was underlying disease in 22 (10.8%) while Wilson disease was observed in 19 (9.4%). Least common underlying reason of CLD leading to development of PHT was biliary atresia seen in 6 (3%) of cases, other aetiologies are described in (Table-3). Average duration of liver disease was 2.87±2.07 years. Fifteen patients were included in Positive group, i.e., with HPS vs 188 in negative group were tested negative for evidence of HPS. Clinical and laboratory parameters in order of percentage in positive group were hypoxia and cyanosis in 100% & 93.3% followed by dyspnoea and grade 4 clubbing in 86.6% patients ($p<0.001$). Child scoring was also done in all patients and 6 patients were CHILD score B and 7 were CHILD C making it 40% and 46.6% respectively. Out of 188 patients in Negative group 7 (3.7%) had dyspnoea on presentation while 1 (0.53%) had grade 4 clubbing and none showed evidence of hypoxia or cyanosis ($p<0.001$). Breakdown of child scoring for negative group revealed in order of frequency that 81 were CHILD SCORE C, 50 CHILD SCORE B making it 81%, 26.6% and 1.06 % respectively. (Table-2). Three patients underwent successful liver transplant 7 patients are awaiting LT, 1 patient is developmentally delayed (post birth asphyxia) and is not fit for LT, 2 patients guardians didn't give consent for LT and 1 patient left against medical advice and is lost on follow up, while one patient of biliary atresia and another of CHF with severe cholangitis expired. (Table-1)

Table-1: Clinical Details and laboratory features of patients with HPS (Hepatopulmonary Syndrome)

Age, (Yr)	Gender	Diagnosis	Dyspnoea	Cyanosis	Clubbing	Child-pugh Class	Pulse Oximetry, % at room air	Pulse oximetry % with oxygen	CEE Scan	MAA Ratio, %	Pulmonary Angio-graphy	PaO2, mm Hg	A-a Gradient, mm Hg	Liver transplant Status
4	Female	CLD (Idiopathic)	Yes	Yes	Yes	B	81%	94%	+	41%	Diffuse micro AV malformation	41.8	76.1	listed
1	Male	CLD(PFIC)	Yes	No	Yes	C	99%	100%	+	Not done	Not done	103.3	12.8	Up for transplant
7	male	CLD (idiopathic)	Yes	Yes	No	A	83%	95%	+	Not done	Diffuse AvVmalfor mation	43	71.7	Listed
16	Male	CLD (Budd Chiari Syndrome)	Yes	Yes	Yes	B	77%	85%	+	>70%	Not Done	-	-	Done
8	Male	Biliary Atresia	Yes	Yes	Yes	C	81%	92%	+	Not Done	Not Done	42.4	58.0	Listed But expired
12	Female	CLD (Idiopathic)	Yes	Yes	Yes	C	79.5%	89%	+	Not Done	Not Done	-	-	Listed
14	Male	CLD (Auto-immune)	Yes	Yes	Yes	B	79%	93.1%	+	51%	Not Done	-	-	Done
15	Female	CLD (Wilson)	Yes	Yes	Yes	C	81.7%	93%	+	Not done	Not Done	42.1	76.4	Listed
9	Female	CLD (Idiopathic)	No	Yes	Yes	C	82.9%	94%	+	Not done	Not done	41.1	50.5	Listed/left against medical advice
11	Male	CLD(Idiopathic)	No	Yes	Yes	B	88.7	99%	+	Not done	Not DOne	53.5	56.5	Listed
9.5	Female	CLD (Idiopathic)	Yes	Yes	Yes	B	79%	88%	+	Not Done	Not Done	-	-	Listed
8	Male	CLD (Idiopathic)	Yes	Yes	Yes	B	78%	86%	+	70%	Not Done	-	-	Done
12	Male	CHF	Yes	Yes	Yes	NA	88%	96%	+	Not Done	Not Done	-	-	Listed but Expired
12	Female	Portal Vein Thrombosis	Yes	Yes	Yes	NA	92%	99%	+	Not Done	Not Done	64.2	57.9	Listed
1.5	Male	CLD (Idiopathic)	Yes	Yes	No	B	89%	97%	+	Not Done	Not Done	45.1	56.5	Not fit

Table-2: Clinical profile of patients of two groups with Portal Hypertension

Parameters		Positive group (n=15)	Negative group (n=188)	*p* value
Dyspnoea		13	7	<0.001
Cyanosis		14	0	<0.001
Grade 4 clubbing		13	1	<0.001
Hypoxia		15	0	<0.001
Child pugh score	A	0	2	0.667
	B	6	50	
	C	7	81	
	None of the Above	2	54	

Positive Group: Presence of Hypoxia. **Negative Group:** Absence of hypoxia

Table-3: Epidemiology and aetiological breakdown of the study group

Characteristics	Values
Age (years) Mean, Standard Deviation	8.76±3.69
Gender, n (%)	
Male	111(54.7%)
Female	92(45.3%)
Duration of liver disease (years) (Mean, Standard Deviation)	2.87±2.07
Diagnosis, n (%)	
Portal Vein Thrombosis	48(23.6%)
Idiopathic Chronic Liver Disease	46(22.7%)
Hepatocaval Syndrome	33(16.3%)
Wilson`s Disease	22(10.8%)
Budd Chairi Syndrome	19(9.4%)
Autoimmune Hepatitis	10 (4.9%)
PFIC	10(4.9%)
CHF	9(4.4%)
Biliary Atresia	6(3%)

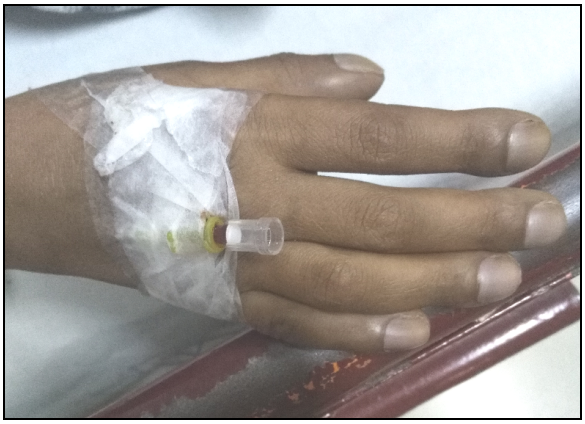

Figure-1: Grade 4 clubbing in patient with Hepto-pulmonary Syndrome

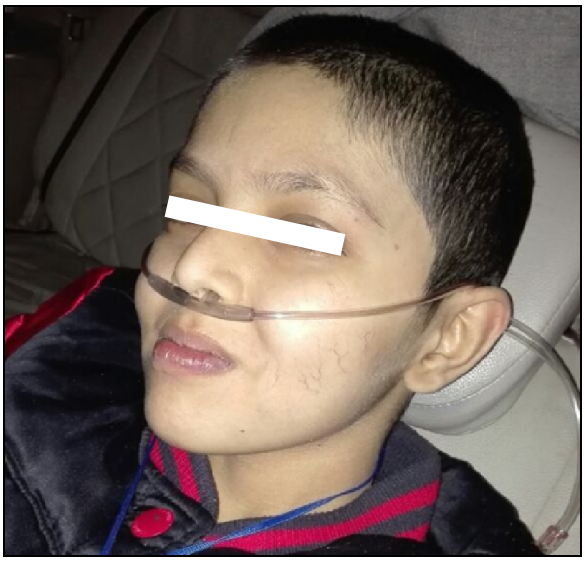

Figure-2: Peripheral Cyanosis in patient with Hepatopulmonary Syndrome

DISCUSSION

Hepatopulmonary syndrome (HPS) is a severe pulmonary vascular complication of chronic liver disease requiring liver transplant. It leads either to diffuse, dilatations involving microscopic pre-capillary and capillary of pulmonary vascular bed or discrete, macroscopic arteriovenous communications resembling classic pulmonary arteriovenous malformations.[10] Of the two variants described in literature, diffuse type is commonest. The less common, type 2 pattern of HPS, does not respond to oxygen therpy.[10]

Progressive dyspnoea and cyanosis are the most frequent symptoms of HPS.[11] Other less common are fatigue, spider nevi, digital clubbing, platypnea, and orthodeoxia.[12] Upright position may lead to the worsening of the dyspnoea and hypoxemia, due to vasodilatation in the basal parts of the lung & thus leads to an increase in ventilation-perfusion mismatch.[12] No symptom or sign is specific to HPS, but if the patient has hypoxemia and digital clubbing along with liver disease, HPS should be considered.[12]Hpoxemia, dyspnoea and grade 4 digital clubbing were consistent features of patients in our positive group. 4 genes, i.e., angiopoetin, endostatin, TIE-1 &endoglin are associated with vascular structure being derived from single nucleotide polymorphism, is related to development of HPS.[13] Classically Hepatopulmonary syndrome (HPS) has an association with portal hypertension with or without cirrhosis, but it has also be seen in patients with acute or chronic hepatitis, hypoxic hepatitis,[14] extra hepatic obstruction, Budd-Chiari Syndrome, and cavopulmonary shunts.[15] Most patients with Hepatopulmonary syndrome (HPS) have severe liver dysfunction and portal hypertension (PHT), however respiratory problems can predominate sometimes.[16] As in our case 1, a 4-year-old girl presented to the cardiology department initially with dyspnoea and central cyanosis. Krowka *et al*[17]reported, 82% of the patients with chronic liver disease showing clinical manifestations of HPS. Hepatopulmonary syndrome is not related to the severity of liver disease, but rather to the presence of PHT.[18] Looking at these facts, it seems mandatory that All patients with chronic liver disease should get a routine measurement of SpO2 with pulse oximetry. The standard procedure is to check it in a child breathing room air in a sitting & then standing position.[19] The threshold for the identification of hypoxemia is 96% [20]previously it was taken as 93%.[21] An arterial blood gas should be done in order to get the PaO2 and determine the arterial- alveolar (A-a) O2 gradient. The cut-off value for the diagnosis of HPS is >15 mm Hg.[21] To demonstrate intrapulmonary shunting, we performed contrast enhanced Echo (CEE) and where available 99 mTc-MAA perfusion lung scan in our patients. D Erge & colleagues used the same methodology to determine intrapulmonary shunting in their case series.[21]

The European Respiratory Society Task Force on pulmonary-hepatic vascular disorders has also recommended CEE as the first-line screening modality.[21] However for diagnosis of shunts in HPS,99 mTc-MAA perfusion lung scan is more sensitive than CEE. Due to its ability to detect small shunts whereas CEE has no quantitative aspect and can miss smaller shunts.[21] On the basis of intrapulmonary shunting, calculated by 99 mTc MAA pulmonary scintigraphy: HPS falls into three grades, mild (shunt ratio <20%), moderate (shunt ratio ≥20% and ≤40%) and severe (shunt ratio >40%).[21] 99 mTc-MAA scans can predict outcomes after LT, depending upon the severity of the shunt.[21] Our 1-year-old patient case of ESLD due to PFIC under process for liver transplant. His oxygen saturation in room air was 96%, his contrast-enhanced echo favoured our suspicion of HPS. It is also reported in literature that 9.7% of 31 normoxaemic patients, had a positive CEE, before transplant. Hence CEE may be positive despite normal arterial blood gases.[22]

As Pulmonary angiography is an invasive method, it is not commonly used in diagnosis of HPS. In our study, pulmonary angiography was performed in only 2 patients, revealing or unmasking diffuse pattern of micro-AV malformation involving both lungs, which is also reported to be the common pattern for HPS. Recently W. De Jesus-Rojas et el reported a case of Caroli Syndrome with hepatopulmonary syndrome.[23] We had 1 patient of congenital hepatic fibrosis 12 years old boy who

developed hepatopulmonary syndrome. He was advised OLT but family couldn't decide and he expired during an episode of cholangitis, which he developed at home and was brought in ER in a critically sick condition.

There was a study in which Swanson KL and colleagues compared the survival rates among HPS and non-HPS patients who had similar liver function; it was shown that median survival was 24 months (5-year survival of 23%) in HPS group and 87 months (5-year survival of 63%) in non-HPS group.[11] It is also reported that almost 50% of patients died within 41 months after diagnosis of HPS.[24] Liver transplantation (LT) is the only proven therapy for patients with HPS.[25] There was either a significant improvement or complete resolution in hypoxemia reported in 85% of patients post transplant in one study.[11] Our 3 patients so far have undergone successful liver transplant while one is up for it. All the three patients showed dramatic improvement in terms of hypoxemia and other clinical sign and symptoms. It has been reported that a complete resolution after LTmay take upto year.[25]Our patients became oxygen independent approximately within6 to 8 weeks post transplant.

Strongest predictors of postoperative mortality are preoperative PaO2 of <50 mmHg in room air and a MAA shunt fraction of ≥30%.[26] Our index case # 4 had a shunt ratio of more than 70% He was on home oxygen therapy, pre transplant. To minimize risk of polycythaemia, Supplemental oxygen before LT can be given, it alleviates subsequent risk of vascular thrombosis as well.[27] Post transplant he developed small intracranial bleed secondary to hypertensive encephalopathy (PRES). He remained ventilated for 20 days and received inhaled nitric oxide for initial 10 days followed by sildenafil, arginine and tab garlic. It is documented that the use of inhaled nitric oxide, Trendelenburg positioning and high frequency ventilation can facilitate better ventilation-perfusion matching post-LT in selected circumstances and improve oxygenation.[15] In some complicated paediatric HPS cases, Post-LT ECMO (Extracorporeal membrane oxygenation) has been successfully used.[28] Our other patient with a shunt ratio of 70% developed hepatic artery thrombosis, required hepatic artery recanalization with thrombolysis subsequently. Available Palliative treatment for patients of Hepatopulmonary syndrome (HPS) unfit for LT candidates could be localized resection or coil embolization of the dilated pulmonary vessels.[29] Different pharmacological agents including, Garlic (Allium sativum),[30] methylene blue, N (G)- nitro-L-arginine methyl ester (L-NAME), curcumin, terlipressin, somatostatin analogues can be used they decrease NO production and down regulate angiogenesis[10] New markers to detect Hepatopulmonary syndrome (HPS)are vascular cell adhesion molecule 1, intercellular cell adhesion molecule 3, and VonWillebrand factor, although have not been tested in large groups.[31]

CONCLUSION

All children with CLD and/or PHT with unexplained dyspnoea, cyanosis and grade 4 clubbing, Hepatopulmonary syndrome (HPS) should be suspected. It is an indication for EARLY liver transplant even in the absence of liver failure. Picked up early it significantly improves post liver transplant outcome, as the severity of pre-LT hypoxemia correlates directly with the length of time needed for HPS resolution post-LT.

AUTHORS' CONTRIBUTION

IM: Literature search, write-up. HA: Conceptualization of study design. HS: Data collection, analysis. NS: Proof reading.

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