Original Research Article

Clinical study on pulmonary artery hypertension in patients with chronic liver disease with portal hypertension

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International Archives of Integrated Medicine, Vol. 6, Issue 11, November, 2019.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 18-10-2019 **Accepted on:** 22-11-2019
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: Rekha NH, Sushmitha P. Clinical study on pulmonary artery hypertension in patients with chronic liver disease with portal hypertension. IAIM, 2019; 6(11): 9-13.

Abstract

The liver is a unique organ as it is connected in series between the portal system and the lung. In patients with chronic liver disease with portal hypertension, constituents of venous blood arising from both the liver and portal system can directly injure the pulmonary vascular endothelium. Pulmonary vascular complications in chronic liver disease with portal hypertension have long been documented in the form of Porto Pulmonary Hypertension (POPH) and hepatopulmonary syndrome (HPS), contributing to morbidity and mortality of patients. Porto pulmonary hypertension is still underdiagnosed entity in patients diagnosed with cirrhosis of liver. We assessed 42 patients with chronic liver disease with portal hypertension 2D Echo Cardiography and doppler study. In our study we observed 15 patients had pulmonary artery hypertension and these patients had mild to moderate TR. Most of our patients with pulmonary hypertension presented with exertional dyspnea.

Key words

Porto pulmonary hypertension, Cirrhosis, Liver disease.

Introduction

Chronic liver disease (CLD) is common medical condition that we come across in medical wards and outpatient department. CLD is one of the common causative conditions for development of portal hypertension. Most of the patients with CLD with portal hypertension are known to develop complications like ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome and hepatopulmonary syndrome which are solely responsible for mortality and morbidity of these patients. The

pathogenesis of all these complications is multifactorial. Pulmonary Arterial Hypertension (PAH) in patients with CLD with or without portal hypertension is commonly under recognized. Most of the times this entity is over looked though there are many mechanisms has been responsible for the development of PAH in these patients, still it requires a high index of suspicion or strong efforts needed to identify this complication among them. POPH is best defined as pulmonary arterial hypertension (PAH) associated with portal hypertension, whether or not portal hypertension is secondary to an underlying liver disease [1].

Diagnostic criteria for portopulmonary hypertension

1. Presence of portal hypertension
   - suggested by the presence of splenomegaly, thrombocytopenia, esophageal varices, portosystemic shunt
   - confirmed by hemodynamic measurements
2. Mean pulmonary artery pressure more than 25 mmHg
3. Pulmonary vascular resistance 240 dynes/cm
4. Pulmonary capillary wedge pressure <15 mmHg

The concept of portopulmonary hypertension has been defined recently. But this condition is still under diagnosed among patients with chronic liver disease with portal hypertension. This under diagnosis of POPH could be due to similar clinical features like edema, ascites which are present in both conditions. There are not much studies about incidence and prevalence of POPH. POPH shares the common pathological changes described for group 1 pulmonary artery pressure. The World Health Organization now recognizes the diagnosis of POPH as a distinct entity. Hemodynamically it is defined as MPAP >25 mmHg and with normal volume status or pulmonary capillary wedge pressure (PCWP) <15 mmHg in patients with chronic liver disease. It has been observed in previous studies that clinical manifestations of portal hypertension typically precede those of pulmonary artery hypertension by 2-15 years [1]. The most common symptoms of POPH include dyspnea upon exertion, syncope, chest pain, fatigue, hemoptysis and orthopnea. No clear mechanism for the development of pulmonary hypertension in patients presenting with portal hypertension. It is considered that this condition has a multifactorial origin. One hypothesis postulates that the hyperdynamic status seen in patients with portal hypertension can cause an increased shear stress at the level of the pulmonary vasculature. Because of these shear stress, vascular remodeling occurs and further changes can lead to development of pulmonary arterial hypertension. Add on to all these changes at vascular levels, most other important mechanism will be the presence of portosystemic shunts allows different vascular mediators that bypass liver metabolism creating an imbalance between vasoconstrictor and vasodilator factors at the level of pulmonary vasculature. Mediators such as endothelin-1, thromboxane A2, Vasoactive Intestinal Peptide (VIP), and serotonin can have direct vasoactive and mitogenic effects also can cause damage to the pulmonary endothelium [2, 3, 4]. Based on hemodynamic study portopulmonary hypertension is classified into three categories [5] (**Table - 1**).

Clinicians must have a high index of suspicion when evaluating patients with liver disease, since POPH itself typically produces no symptoms or only has symptoms related to the underlying cirrhosis or portal hypertension. Here we conducted study on 42 patients diagnosed to have cirrhosis by clinical history and by ultrasound, at Raja Rajeswari Medical College and Hospital, Bangalore.

Materials and methods

Study design: This was observational study done at Raja Rajeswari Medical College and Hospital, between October 2018 to April 2019.

Table – 1: Diagnostic criteria and staging for portopulmonary hypertension			
	Mean Pa mmHg	Mean P pcwp mmHg	PVR dynes cm
Mild	>25 to <35	<15	>240
Moderate	>35 TO <45	<15	>240
Severe	>45	<15	>240

Patients with clinical diagnosis of chronic liver disease from medical wards and medicine outpatient department were included in the study. Informed written consent was obtained from participants of the study. Institutional ethical committee clearance was obtained before the study.

Inclusion criteria

- Patients with clinical diagnosis of chronic liver disease
- Patients with ultrasound diagnosis of cirrhosis.
- Age group between 18 -55years

Exclusion criteria

Patients with h/o smoking, previous h/o cardiac illness, congestive cardiac failure, previously diagnosed with pulmonary hypertension, previous h/o congenital heart disease, cardiomyopathies, valvular heart diseases, Budd Chiari syndrome, portal vein thrombosis.

Patients who met with inclusion criteria are subjected for ultrasound abdomen examination. Various blood tests were done including liver function tests, complete hemogram, peripheral blood smear, markers for viral hepatitis, transthoracic Echocardiography and doppler study, prothrombin time, serum ammonia levels.

Results were analyzed by suitable statistical parameters.

Results

We conducted study on 42 patients with chronic liver disease diagnosed clinically and by ultrasound abdomen. In our study, we found male predominance. We observed maximum number of patients were in age group 41-50 years (34%) followed by 30-40 years (29%), and 51-60 years (22%). Chronic alcohol consumption history was there in majority of patients. Majority of patients presented with history of distension of abdomen followed by jaundice and pedal edema. Very few patients had bleeding manifestations. Majority of patients had h/o alcohol consumption for more than 10 years. Nearly 92% of patients were anemic, macrocytic anemia was observed in 56% of patients. 24% of patients had thrombocytopenia. Nearly 68% of patients had prolonged prothrombin time. Out of 42 patients, 15 patients had pulmonary Artery Hypertension (PAH). Mild to moderate TR was observed in most of patients with PAH. Among 15 patients with PAH 12 patients were nonsmokers. Only 3 patients had h/o smoking. 13 patients had mild pulmonary hypertension and 2 patients had moderate to severe pulmonary hypertension. These patients had persistent pedal edema and NYHA grade 4 dyspnea. We observed patients with mild pulmonary hypertension had pedal edema. Recent worsening of dyspnea was important finding in patients with POPH in our study. In patients with CLD with portal hypertension diagnosed with POPH, symptoms like edema and ascites were less responsive to usual dose of diuretics compared to other patients without pulmonary hypertension. This observation was significant in our study (**Table – 1, 2**).

Table - 1: ECHO PAH distribution of patients studied.

ECHO PAH	**No. of patients**	**%**
Normal	26	63.0
Mild	13	31.7
Moderate	1	2.4
Severe	2	4.9
Total	41	100.0

Table - 2: PAH distribution of patients studied.

PAH (in mmHg)	No. of patients	%
No	26	63.4
>25 to37 (mild)	13	31.7
37-44 (mod)	2	2.4
>44 (severe)	2	4.9
Total	41	100.0

Discussion

In present study, we observed pulmonary artery hypertension was observed in 15 patients out of 42 patients. We observed prevalence of 36% of PAH in our patients. In our study we found, prevalence of PAH was more compared to other previous studies. In a study done by Hui-Song Chen, et al. [6] of the 100 patients enrolled in their study, 10 were diagnosed with POPH. Seven of the cases were mild, two were moderate and only one was severe. In our study we found, 13 patients had mild pulmonary hypertension and 2 patients had moderate to severe pulmonary hypertension. Those patients with severe PAH had persistent pedal edema and NYHA grade 4 dyspnea. We observed patients with mild pulmonary hypertension had pedal edema, worsening of exertional dyspnea was a prominent feature in them. We observed mild PAH was observed is majority of patients. We found there was history of chronic smoking among 3 patients in our patients. Majority of our patients presented with symptoms of chronic liver disease with portal hypertension. From our study results showed that the severity of POPH is unrelated to liver function, as we were unable to identify an association between POPH severity and Child-Pugh class, even previous studies were unable to find correlation between severity of PAH and severity of liver disease. However, this conclusion is based only on small number of cases. Larger studies are required to verify this correlation. In the early stages of disease, patients may be asymptomatic or oligosymptomatic. The clinical symptoms of the underlying liver disease or portal hypertension may be present. There are no known clinical factors that determine the risk of POPH in patients with advanced liver disease. The first clinical symptom experienced by patients with POPH is usually dyspnea on exertion. Since presence of ascites also causes dyspnea in these patients most of the times condition can go underrecognized. Dyspnea on exertion is the most common presentation complaint, but it is acknowledged most of the times to related to other conditions such as refractory ascites with mechanical thoracic impairment, hepatic hydrothorax, anemia and sarcopenia/ deconditioning [7, 8].

Other common symptoms include fatigue, generalized weakness, lightheadedness and orthopnea [9]. The single most important test to screen for POPH is the two dimensional transthoracic echocardiogram (TTE). The ESC guidelines recommend TTE screening in all symptomatic patients with liver disease. POPH causes progressive stress to the right ventricle, leading to right ventricular dysfunction, progressive chronic cor pulmonale and eventually death [10].

The degree of right ventricular dysfunction correlates highly with survival and mortality in patients with POPH. An earlier study by Robalino, et al. showed a poor 1-yr survival of 40% [11].

When compared to patients with idiopathic PAH, patients with POPH have a worst survival profile, with a 3year survival of only 38% versus 78% for idiopathic PAH [11].

Conclusion

Portopulmonary hypertension is becoming a well-recognized subtype of pulmonary arterial hypertension. It represents a complication of liver disease although it can develop in patients who only present with portal hypertension and no structural liver alterations. Since PAH in cirrhotic patients can aggravate mortality and morbidity. In view of prognosis of the underlying clinical condition all of us need to identify POPH in patients with chronic liver disease. Clinicians must maintain a high index of suspicion when

evaluating patients with liver disease, since POPH itself typically produces no symptoms or only has symptoms related to the underlying cirrhosis or portal hypertension.

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