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ORIGINAL ARTICLE

Prevalence and predictors of hepatopulmonary syndrome in liver transplant candidates

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KEYWORDS

Hepatopulmonary syndrome;
Liver transplantation;
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Abstract *Background:* Hepatopulmonary syndrome (HPS) is an independent predictor of survival after liver transplantation. Although the prevalence of chronic liver diseases is high in Egypt, the frequency of HPS among liver transplant candidates (LTC) is unknown.

Aim: To assess the frequency of HPS and factors predictive of diagnosis of HPS in patients with end-stage liver diseases who are LTC.

Methods: A cross sectional study of patients with end stage liver diseases who are LTC. Patients were subjected to clinical examination, laboratory investigations, arterial blood gas (ABG) measurement, pulmonary function tests, upper gastrointestinal endoscopy, and transthoracic contrast enhanced echocardiography (TCEE). The severity of liver disease was assessed by Model for end-stage liver disease (MELD) score. The diagnostic criteria for HPS were intrapulmonary vascular dilatation (IPVD) documented by TCEE, and alveolar-arterial oxygen gradient (A-aDO_2) $\geqslant$15 mmHg.

Results: Eighty-four LTC patients were enrolled in the study. Sixteen patients (19%) fulfilled the criteria for diagnosis of HPS. Patients with HPS showed older ages, longer duration of liver diseases which were more severe (MELD score). Dyspnoea, cyanosis, clubbing, platypnoea, spider naevi and features of portal hypertension were significantly more common in the HPS group. In the recumbent position; patients with HPS had a significantly lower PaO_2 and larger A-aDO_2 compared to those without HPS. Patients with HPS showed a further fall in their PaO_2 on sitting up (orthodeoxia).

Conclusions: The prevalence of HPS among the studied group of Egyptian liver transplant candidates is 19%. Cyanosis, clubbing, spider naevi and platypnoea–orthodeoxia are suggestive indicators of HPS.

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Introduction

Egypt has the highest countrywide prevalence of hepatitis C virus (HCV) infection in the world [1]. Twenty percent of those with HCV-hepatitis progress to end stage liver cirrhosis [2]. Liver transplantation is a treatment option for end stage liver cirrhosis. In cases of liver disease with an indication for transplantation, vascular disorders such as hepatopulmonary syndrome (HPS) may develop as a result of hepatocellular dysfunction or portal hypertension [3]. Hepatopulmonary syndrome is associated with a reduced life expectancy [4]. No pharmacological therapy has thus far consistently been effective in improving HPS and the only treatment associated to the reversal of HPS in patients with cirrhosis has been liver transplant and HPS is currently one of the criteria for its anticipation [5]. Being an independent predictor of mortality and morbidity after liver transplantation [4]; HPS plays a role in the assessment and follow-up of liver transplant candidates (LTC) [3].

Hepatopulmonary syndrome is a pulmonary vascular disorder characterized by the triad of chronic liver disease, arterial hypoxaemia and intrapulmonary vascular dilatations (IPVD) [6]. In all patients with chronic liver disease and hypoxaemia, the diagnosis of HPS requires documentation of IPVD. The most common tools are contrast echocardiography and technetium^{99m}-labelled macroaggregated albumin perfusion scanning. The latter technique is used both for the diagnosis of HPS and quantification of the magnitude of shunting [6].

The objective of the present study was to determine the prevalence of HPS in a sample of Egyptian patients with end-stage liver diseases who are LTC; and to compare demographic, clinical, and laboratory characteristics in patients with and without HPS.

Patients and methods

Patients

Adult patients with end stage liver disease who are LTC were selected from outpatient clinics or inpatient wards of the departments of Internal Medicine, Mansoura University Hospitals.

Exclusion criteria

1- Primary pulmonary disease such as chronic obstructive pulmonary disease.
2- Abnormal CXR (e.g. pleural effusion, pneumonia or atelectasis).
3- Heart failure.
4- Patients with smoking history.

Methods

1- *Thorough clinical history and physical examination.*
2- *Blood Tests:* Complete blood picture, urea and creatinine, liver function tests, viral markers for hepatitis C and B.
3- *The Model for End-Stage Liver Disease (MELD) score:* This is a waiting list positioning criteria that is based on liver disease severity [7]. The MELD score ranges from 6 to 40, with higher values indicating more severe disease. This system has ideal model characteristics, since it is based on few parameters (all of them objective). These parameters are easily obtainable and reproducible and provide a score standard with an excellent capability for prognoses regarding the risk of death among LTC [8]. The advantage of this system over the previous system, which used the duration of the wait for the transplant (chronological criterion), lies in the fact that it reduces the mortality rate by prioritizing urgent cases [9]. The MELD score was calculated using the original formula without including the cause of liver disease; MELD score = $0.957 \times \log e$ (creatinine mg/dL) + $0.378 \times \log e$ (bilirubin mg/dL) + $1.120 \times \log e$ (INR) + 6.43.
4- *Upper gastrointestinal endoscopy.*
5- *Abdominal ultrasound:* to confirm the presence of liver cirrhosis and/or portal hypertension.
6- *Arterial blood gas (ABG):* samples were obtained by radial arterial puncture in recumbent position and after being upright for 20 min to detect orthodeoxia "defined as PaO_2 fall by 5% in the upright position as compared to recumbency value [10]".
7- *Spirometry:* performed using a computed spirometer (Jaeger, Germany) to rule out primary pulmonary diseases. Spirometry was performed 3 times and the best effort of FEV_1, FVC and FEV_1/FVC was recorded.
8- *Chest X-ray (CXR]:* to rule out cardiac or pulmonary diseases and to exclude other causes of hypoxaemia such as emphysema or fibrosis.
9- *Transthoracic contrast enhanced echocardiography (TCEE):* Patients with A-a$DO_2 \geqslant 15$ mmHg underwent a TCEE [11]. Apical four-chamber imaging was used for the simultaneous visualization of the atria and ventricles. Peripheral venous access was obtained through the forearm. A three-way stopcock was attached and two 10 mL syringes were connected to the other two ports. One 10 mL syringe was empty (with air removed) and the other was filled with saline solution. The microbubbles were produced manually by flushing the saline solution from one syringe to the other 10 times. The agitated solution was then quickly administered in the peripheral vein with the patient in the upright position and the second-harmonic imaging was performed. The test was considered positive when microbubbles were detected in the left heart chambers between four and six heart cycles following opacification of the right chambers; and was considered negative if there was no passing of microbubbles to the left chambers. Visualization of microbubbles in the left chambers prior to the fourth heartbeat was considered evidence of intracardiac shunt [12]. Three examinations were performed on each patient and each subsequent injection was initiated after the disappearance of the microbubbles from all cavities. The diagnosis of HPS was based on identifying IPVD through TCEE, and A-aDO_2 - $\geqslant 15$ mmHg [12].

Statistical analysis

Quantitative data were expressed as means ± standard deviations while qualitative data were expressed as numbers (per-