ARE THE SPIDER ANGIOMAS SKIN MARKERS OF HEPATOPULMONARY SYNDROME?

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ABSTRACT – Context – Hepatopathies can significantly influence both veins and arteries, these changes may cause some cutaneous stigmas, such as spider angioma (SA) and some systemic vascular changes, such as those observed in hepatopulmonary syndrome (HPS). Based on this common pathophysiological root we can assume that the SA can be skin markers of HPS. Objective – The objective of this study is to assess whether there is a relationship between the presence of SA and HPS. Methods – Records of 40 patients with liver cirrhosis who underwent contrast echocardiography were evaluated, in which we researched the description of SA, physical examination, and other clinical and laboratory data. For diagnosis of HPS we use these signs of the disease: presence of liver disease (cirrhosis in the case), abnormalities in gas exchange by arterial blood gases, and evidence of pulmonary vasodilations by the contrast echocardiography. Results – The SA were found in 21/40 (52.5%) patients and hepatopulmonary syndrome in 9/40 (22.5%). The HPS was observed in 8/21 (38.1%) of patients with SA and 1/19 (5.3%) patients were without this sign (P<0.01). We found no statistically significant difference between the SA and the presence of HPS with sex or age. Patients with SA had a higher hypoxemia [PaO2 84.8 ± 11.5 mmHg and 19.8 ± 14.7 mmHg alveolar-arterial gradient of oxygen (AAG)] than those without SA [PaO2 90.8 ± 10.7 mmHg and 10.9 ± 11.7 AAG mmHg] (P<0.05). Conclusion - Our findings show a correlation between the presence of SA and HPS, suggesting that the SA may be cutaneous markers of HPS.


INTRODUCTION

The hepatopulmonary syndrome (HPS) is an alteration in the vasculature of the lung secondary to a chronic liver disease, usually cirrhosis, characterized by the triad of liver disease, abnormalities in gas exchange (increase of alveolar-arterial gradient of oxygen, with or without hypoxemia) and evidence of intrapulmonary vasodilations (IVD)12, 21, 29, 34.

Liver cirrhosis causes a series of systemic manifestations, including changes in the pulmonary vasculature as idiopathic pulmonary hypertension, anastomoses between the portal circulation and pulmonary and the HPS. The moderate dyspnea is a common finding in patients with liver cirrhosis, may result from compression of lung parenchyma by ascites and/or stroke pleural11, concomitant pathologies that affect the lungs and liver. However, severe hypoxemia (PaO2 <60 mmHg) is less common and, in the absence of associated cardiopulmonary disease, strongly suggests the presence of HPS11, 37.

Hypoxemia [PaO2 < 70 mmHg or increase of alveolar-arterial gradient of oxygen (AAG) ≥ 15 mmHg] is multifactorial, being caused either by intrapulmonary vascular dilations, and by changes in alveolar-capillary diffusion of oxygen and/or the imbalance in the ventilation/alveolar perfusion12, 14, 16, 23, 29.

Still little is known about the pathogenesis of intrapulmonary vascular dilation, it is believed that it is due to a number of factors such as the imbalance between vasoconstrictors and vasodilators substances, and/or increased sensitivity of pulmonary endothelium to a vasodilator and/or hyporesponsiveness to vasoconstrictors substances12, 14, 16, 23, 29.

This imbalance between vasodilator and vasoconstrictor substances, is also involved in the pathophysiology of others vascular abnormalities observed in cirrhosis, such as the clubbing, palmar erythema and SA21, 22.

The SA are lesions that appear as red spots, shiny, with numerous microvascular radiations which pales when pressure on a central spot is temporarily applied2, 5, 15, 23, 32, 36. They may be present in physiological situations, as in pregnancy, on children, on women in use of oral contraceptives, but are commonly asso-
ciated with chronic liver diseases, its prevalence is variable, ranging from 4 to 47% depending on diagnostic criteria and methods used(23).

Assuming that both the HPS and the SA have a common pathophysiological root, that is an imbalance between vasoconstrictor and vasodilator substances, and the suggestion of some authors, that SA are most commonly seen in patients with the HPS, we can assume that SA could be used as skin markers of HPS. This would allow an earlier and less costly diagnosis of the syndrome, and thus a more effective therapeutic approach. This study aims to evaluate if exists a relationship between SA and HPS.

METHODS

We prospectively evaluated 45 patients with liver cirrhosis diagnosis seen at the Gastroenterology and Hepatology Service of the General Hospital of Goiânia. The diagnosis of cirrhosis was based on clinical and laboratory criteria (history, physical examination, ultrasound findings and biochemical data and/or CT scan of the abdomen) and/or histology.

The study included patients of both sexes suffering from chronic liver disease, aged above 18 years old and who voluntarily agreed to participate. These patients underwent a clinical interview and physical examination, focusing on the presence of SA. Blood samples were collected to perform liver function tests, complete blood count. Arterial blood gases were taken with patients sitting and breathing room air. The AAG was calculated using the alveolar gas equation. Subsequently, a simple echocardiography and a contrast echocardiography (CEE) have been made.

The presence of SA was based on physical examination data. We consider as carriers of HPS patients who met the following criteria: presence of chronic liver disease, abnormalities in arterial oxygenation (AAG ≥ 15 mmHg) and evidence of intrapulmonary vasodilations (IVD) the CEE(29).

For the research of IVD we used CEE performed by an experienced researcher using the method of microbubbles. The technique is based on the rapid infusion of 10 mL saline solution (NaCl 0.9%) in the right median cubital vein(33), after its agitation and production of microbubbles. These should be viewed in the right heart chambers, with the help of a transducer positioned in the left parasternal region, since they are echogenic. Under normal conditions, the microbubbles are retained in the pulmonary capillary bed, as in patients with IVD they are displayed in the left atrium in 3 to 6 cardiac cycles after being observed in the right chambers(33). Its appearance before the third cycle suggests the presence of intracardiac communication(33).

Our study was approved by the Ethics Committee of human and animal research of General Hospital of Goiânia.

Statistical calculations were performed using the program Epi Info 3.5.2 (Centers for Disease Control Epidemiology Program Office, Atlanta, Georgia). To evaluate the association between qualitative categorical variables it was used the chi-square test of Pearson, with the Yates test correction when necessary. We used the Kruskal-Wallis test to test the correlation of quantitative independent variables. The results were expressed as mean ± standard deviation (SD) and significance level in all tests was set at 5%.

RESULTS

Of the 45 patients initially evaluated five were excluded (2 because they had atrio-ventricular communication, 2 for not having adequate acoustic window to perform the CEE and one for not having finished the protocol). The 40 (88.9%) remaining patients composed our study group. Of these, 23 (57.5%) were men and 17 (42.5%) women. Our population was composed mostly by whites (65% - 26 patients) and the average age was 48.6 ± 11.7 years old (ranging from 19 to 71 years old).

Patients were divided into two groups according to the presence or absence of SA. Group A: composed of 21 patients (52.5%) with SA, the average age was 48.9 ± 10.1 years old, 13/21 (56.5%) were male. Group B: composed of 19 patients (47.5%) without SA, the average age was 48.3 ± 13.6 years old and 10/19 (43.5%) were male. There was no statistically significant difference between these variables. Table 1 summarizes the demographics data of the researched population.

TABLE 1. Characteristics of the 40 patients divided according to the presence of spider veins

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A Spider Veins</th>
<th>Group B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>21 (52,5%)</td>
<td>19 (47,5%)</td>
<td></td>
</tr>
<tr>
<td>Average of age (years)</td>
<td>48,9 +/- 10,1</td>
<td>48,3 +/- 13,6</td>
<td>0,6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (56,5%)</td>
<td>10 (43,5%)</td>
<td>0,7</td>
</tr>
<tr>
<td>Female</td>
<td>8(47,1%)</td>
<td>9 (52,9%)</td>
<td>0,7</td>
</tr>
<tr>
<td>Average of PaO2 (mmHg)</td>
<td>84,8 +/- 11,5</td>
<td>90,8 +/- 10,7</td>
<td>0,04</td>
</tr>
<tr>
<td>Average of AAG (mmHg)</td>
<td>19,8 +/- 14,7</td>
<td>10,9 +/- 11,7</td>
<td>0,01</td>
</tr>
<tr>
<td>Echocardiography:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>6 (28,6%)</td>
<td>15 (78,9%)</td>
<td>0,005</td>
</tr>
<tr>
<td>With IVD without HPS</td>
<td>7 (33,3%)</td>
<td>3 (15,8%)</td>
<td>0,005</td>
</tr>
<tr>
<td>With HPS</td>
<td>8 (38,1%)</td>
<td>1 (5,3%)</td>
<td>0,005</td>
</tr>
<tr>
<td>HPS</td>
<td>8 (38,1%)</td>
<td>1 (5,3%)</td>
<td>0,03</td>
</tr>
<tr>
<td>IVD</td>
<td>15 (71,4%)</td>
<td>4 (21,1%)</td>
<td>0,004</td>
</tr>
</tbody>
</table>

PaO2 = partial pressure of arterial oxygen; HPS= Hepatopulmonary Syndrome; IVD = intrapulmonary vasodilations; AAG = alveolar-arterial gradient of oxygen

176 Arq Gastroenterol v. 50 no. 3 - jul./set. 2013
The IVD were present in 19/40 (47.5%), and in 9/40 (22.5%) also met the other criteria for HPS.

When comparing the two groups we observed that the IVD were present in 15/21 (71.4%) patients of group A and in 4/19 (21.1%) patients of group B (P<0.005), with a relative risk 3.4 (1.3 to 8.4). About the HPS, it was present in 8/21 (38.1%) and in 1/19 (5.3%) respectively (P<0.05), with a relative risk of 5.2 (0.8 to 33.9). The mean PaO2 and AAG were respectively 84.8 ± 11.5 mmHg and 19.8 ± 14.7 mmHg in group A and 90.8 ± 10.7 mmHg and 10.9 ± 11.7 in group B (P<0.05).

Most patients 36/40 (90%) had a Child-Pugh index, which does not allow to evaluate relations of SA with the severity of liver disease.

The hepatitis C virus isolated or associated with alcohol consumption were the most common etiologic agents of cirrhosis, present in 23/40 (57.5%) and 18/40 (45.0%) respectively. There was no statistically significant difference between the presence of SA and the etiology of cirrhosis (P = 0.68) (Table 2).

**TABLE 2. Correlation between the presence of spider veins and cirrhosis etiology**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Spider angioma</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>21 (52.5%)</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td>HCV</td>
<td>8 (38.1%)</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5 (23.8%)</td>
<td>5 (23.8%)</td>
</tr>
<tr>
<td>Alcohol and virus</td>
<td>5 (23.8%)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>HBV</td>
<td>1 (4.8%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>0</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>1 (4.8%)</td>
<td>1 (5.3%)</td>
</tr>
</tbody>
</table>

HCV = hepatitis C virus; HBV = hepatitis B virus

**DISCUSSION**

Galen’s view that the liver controls blood in the veins lost prestige as the true nature of the vascular system was becoming evident. However, information obtained from the study of patients with liver disease have revealed that these diseases can significantly influence both the arteries and veins.

In chronic liver disease we can observe the influence of portal hypertension in the vascular system. There is dilatation of the veins of the thorax and abdomen and formation of collateral circulation between portal and systemic circulation, because of the opening and dilation and hypertrophy of preexisting vascular channels.

Ectopic varicose veins may occur in the digestive tract. We can observe the presence on skin of SA, most commonly on the face and upper chest, the palms of the hands may become hyperemic (palmar erythema) and we can find cyanosis, edema in the nail bed and it subsequently can rise to the digital clubbing.

The SA are known to be a cutaneous stigma of chronic liver disease, occurring in approximately 15% of patients with Laennec’s cirrhosis. In patients with this sign, esophageal varicose veins and collateral circulation in the abdomen appear to be two times more frequent.

In the pulmonary vasculature we can also observe changes resulting from chronic liver disease. Idiopathic pulmonary hypertension can arise, anastomoses between the portal and the pulmonary circulation and HPS.

The pathogenesis of intrapulmonary vascular dilatation is still debated, several mechanisms have been proposed, including: imbalance between vasoconstrictors and vasodilators substances; the increase of pulmonary endothelium sensitivity to a vasodilator not produced or not metabolized by the diseased liver, or even hyporesponsiveness to vasoconstrictor substances.

Among the vasodilator substances postulated to explain the pathogenesis of HPS, the nitric oxide (NO) wins a role. The NO is a potent endothelial vasodilator and could be responsible for intrapulmonary vasodilatation, since in cirrhotic patients the serum levels of this substance are elevated, possibly due to endotoxemia observed in this group of patients, which would induce an increased production of NO.

Therefore, both the HPS and the SA seem to have a common pathophysiological root, which is the imbalance between vasoconstrictor and vasodilators substances.

Some authors have suggested that the SA is most commonly seen in patients with the HPS, although other authors have not found the same relationship. In the classic story of Rydell and Hoffbauer the authors have called attention to the fact that the vast majority of cirrhotic patients with cyanosis and digital clubbing associated exhibit one or more vascular stigmas of cirrhosis, especially SA. Andrivet et al. found the signal in seven of nine cirrhotic patients with hypoxemia. Rodriguez-Roisin et al. demonstrated that patients with SA have higher gas exchange abnormalities, reduced pulmonary vasoconstriction response to hypoxia, reduced pulmonary vascular resistance and systemic and major changes in the relation ventilation/perfusion than patients without the sign.

In contrast, Lima et al. evaluating the clinical features of cirrhotic patients candidates for liver transplantation, observed the SA in 8/9 (88.8%) of patients with HPS and in 35/47 (74.5%) of cirrhotics without the syndrome (P = 0.6). Fallon et al. also evaluating candidates for liver transplantation, also found no difference in the prevalence of SA in patients with or without HPS (37% and 39% respectively, P = 0.78). In our study, the SA were found in 8/9 (88.9%) patients with HPS, in 7/10 (70.0%) of patients with IVD without hypoxemia and in 6/21 (28.6%) of patients without IVD (P<0.005). Suggesting that the SA could not only be related to HPS but as well as to the degree of IVD, and may also be a predictive marker of HPS.

The HPS is a respiratory manifestation of liver disease characterized by the triad: liver disease, hypoxemia, and IVD. In the present study, we found the IVD in 15 (71.4%) of 21 patients with SA and in 4/19 (21.1%) of those without
such abnormalities \((P<0.01)\). Mohammad Alizadeh AH et al.\(^{(25)}\) found the presence of IVD in 17/54 (31.4\%) of researched patients, of these, 10/54 (18.3\%) met criteria for the HPS and 7/54 (13\%) had only IVD, defined as subclinical cases of the syndrome. In this study, HPS was found in 9/40 (22.5\%) patients. Despite that, 10/40 (25.0\%) patients had IVD, however, without fulfilling the diagnostic criteria of the syndrome, which may represent a frustrated form of it, as the subclinical cases found in the study of Mohammad Alizadeh AH et al.\(^{(25)}\).

The average of PaO2 was lower in patients with SA (84.8 ± 11.5 mm Hg) compared with patients without the sign (90.8 ± 10.7 mm Hg) with \(P<0.05\); and the average AAG in the first group was higher (19.8 ± 14.7), compared with 10.9 ± 11.7 in the second \(P<0.05\). These findings suggest that patients with SA are more hypoxemic than patients without SA.

Based on our findings we suggest that the SA are skin markers of the presence of HPS. However, it is necessary to perform further studies to correlate the presence of HPS with the number and size of the SA.


RESUMO – Contexto - As hepatopatias podem influenciar de forma considerável tanto as veias quanto as artérias, dessas alterações podem surgir alguns estigmas cutâneos, como as aranhas vasculares (AV) e algumas alterações vasculares sistêmicas, como as observadas na Síndrome Hepatopulmonar (SHP). Baseados nessa possível raiz fisiopatogênica comum, podemos supor que as AV sejam marcadores cutâneos da SHP. Objetivo - Avaliar se há relação entre a presença das AV e a SHP. Métodos - Foram avaliados os prontuários de 40 pacientes com cirrose hepática submetidos a ecocardiografia com contraste (ECC), nos quais pesquisamos a descrição de AV, no exame físico, e outros dados clínicos e laboratoriais. Para diagnóstico da SHP utilizamos os seguintes critério: presença de hepatopatia (no caso cirrose), de anormalidades nas trocas gasosas pela gasometria arterial, e evidências de vasodilações pulmonares pela ecocardiografia com contraste. Resultados - As AV foram encontradas em 21/40 (52,5\%) pacientes e a síndrome hepatopulmonar em 9/40 (22,5\%). A SHP foi observada em 8/21 (38,1\%) dos pacientes com AV e em 1/19 (5,3\%) dos pacientes sem esse sinal \((P<0.01)\). Não encontramos diferença estatisticamente significativa entre a presença das AV e da SHP com sexo ou faixa etária. Pacientes com AV apresentaram maior hipoxemia (PaO2 84,8 ± 11,5 mmHg e GAA 19,8 ± 14,7 mmHg) que os sem AV (PaO2 90,8 ± 10,7 mmHg e GAA 10,9 ± 11,7 mmHg) \((P<0.05)\).

Conclusão - Nossos achados mostram correlação entre a presença das AV e a SHP, sugerindo que as AV possam ser marcadores cutâneos da SHP. DESCRIPTORES – Hepatopatias, complicações. Dermatopatias vasculares. Síndrome Hepatopulmonar.
REFERENCES