Intrapulmonary Vascular Dilatation Evaluated by $^{99m}$Tc-MAA Scintigraphy and Its Association with Portal Hypertension in Schistosomiasis

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Abstract

Background: Portal hypertension is responsible for various complications in patients with schistosomiasis, among them intrapulmonary vascular dilations (IPVD). In cirrhotic patients, the presence of IPVD is a sign of poor prognosis, but in patients with hepatosplenic schistosomiasis (HSS) there are no studies assessing the significance of this change. The aim of this study was to evaluate the occurrence of IPVD through $^{99m}$Tc-MAA scintigraphy in patients with HSS and its relationship with clinical, laboratory, endoscopic and ultrasound parameters.

Methods: Cross-sectional study evaluating 51 patients with HSS. Patients were diagnosed with IPVD when the brain uptake of $^{99m}$Tc-MAA was higher than 6%. Subsequently, they were divided according to presence (G1) or absence (G2) of IPVD and variables were compared between groups.

Results: Overall, 51 patients with mean age of 56±12 years were assessed. IPVD was observed in 31 patients (60%). There was no statistically significant differences between groups when clinical, laboratory and endoscopic parameters were compared. Regarding ultrasound parameters, the splenic vein diameter was smaller in G1 (0.9±0.3 cm) compared to G2 (1.2±0.4 cm), p = 0.029.

Conclusion: In patients with HSS, the occurrence of IPVD by $^{99m}$Tc-MAA scintigraphy was high and was associated with lower splenic vein diameter, which can be a mechanism of vascular protection against portal hypertension. However, more studies are needed to determine the clinical significance of the early diagnosis and natural evolution of IPVD in this population.

Introduction

Hepatosplenic schistosomiasis (HSS) is characterized by the presence of liver fibrosis around the intrahepatic branches of the portal vein without damage to the hepatocyte synthesis ability [1]. It is estimated that schistosomiasis affects 2.5–6 million Brazilians [2] and about 10% of them develop the hepatosplenic form, which is the main cause of portal hypertension in Northeastern Brazil [3]. Portal hypertension is responsible for a number of complications in patients with schistosomiasis, like esophageal varices, gastrointestinal bleeding or intrapulmonary vascular dilatation (IPVD) [4,5].

IPVD is the key event in the development of hepatopulmonary syndrome (HPS), when associated with alveolar-arterial difference of $O_2 > 15$ mmHg and liver disease with portal hypertension [6]. The natural history of IPVD has not been sufficiently understood, since its precise pathogenic mechanism remains unclear, but portal hypertension may be the initial stimulus for vasodilation [7]. In cirrhotic patients, the presence of IPVD is evidence of poor prognosis, especially when associated to HPS [4], but in HSS patients, there are no studies assessing the clinical significance and prognosis.

The method most widely used to diagnose IPVD is transthoracic Doppler echocardiography [6,8,9]; however, studies have suggested $^{99m}$Tc-macroaggregated albumin ($^{99m}$Tc-MAA) scintigraphy as alternative, for being sensitive, specific and because it quantifies the magnitude of IPVD [10–12]. In $^{99m}$Tc-MAA scintigraphy, radiolabeled particles, which usually have more than 20 μm in diameter, are injected and remain retained in the pulmonary vasculature, since capillaries measure 8 to 15 μm in diameter [12]. In the presence of IPVD, as in vasodilation, a fraction of these particles migrate to the systemic circulation, which can be quantified by radioactivity in the intra- and extrapulmonary circulation [6].

The aim of this study was to evaluate the occurrence of IPVD by $^{99m}$Tc-MAA scintigraphy and its association with clinical, laboratory, endoscopic and ultrasound parameters in patients with HSS.

Materials and Methods

This is a descriptive, cross-sectional study involving intergroup comparisons. Fifty-one consecutive patients in treatment at the
Intrapulmonary vascular dilatation (IPVD) is the key event in development of hepatopulmonary syndrome, an arterial oxygenation defect in patients with portal hypertension. IPVD diagnosis can be made by EchoDopplercardiography or ⁹⁹mTc-macroaggregated albumin scintigraphy (⁹⁹mTc-MAA), and ethiopatogeny is still unknown. In Northeastern Brazil, hepatoplosenic schistosomiasis (HSS) is the main cause of portal hypertension. In cirrhcots, the presence of IPVD influences survival and candidacy for liver transplantation, however, in HSS patients, IPVD has been poorly studied, specially using lung perfusion scan with ⁹⁹mTc-MAA. Some authors believe that IPVD is common in HSS and in the existence of differences in indirect portal hypertension parameters between patients with and without IPVD. All patients were distributed into two groups according to presence or not of IPVD, and laboratorial, endoscopy and ultrasound tests were performed. Occurrence of IPVD was high and was associated with lower splenic vein diameter, which can be a vascular protection mechanism against portal hypertension status.

For image acquisition, the detector was positioned approximately 10 cm away the patient’s body, using a 120° × 126° matrix for five minutes. Subsequently, the images were analyzed by drawing regions of interest (ROIs) in skull and lungs. Patients were diagnosed with IPVD when the brain uptake of ⁹⁹mTc-MAA was higher than 6% [15].

The brain uptake was calculated using the following formula: \( \frac{\text{geometric mean of brain uptake}/0.13}{\text{geometric mean of brain uptake}} = \frac{0.13}{0.13} \). According to the presence or absence of IPVD, patients were divided into two groups - G1 (positive IPVD) and G2 (negative IPVD) and the clinical (age, sex, history of gastrointestinal bleeding), laboratory, endoscopic and ultrasound features of each group were compared.

To compare quantitative variables, the Mann-Whitney U test was used, which does not need to assume data normality and has power efficiency around 95%. For qualitative variables, the chi-square test was used to verify if the group interferes in the variable being assessed. Differences between groups were considered statistically significant when p-value was <0.05.

Ethic statement

The study was evaluated and approved by the Ethics Research Committee of the Center for Health Sciences - UFPE and all patients signed the informed consent form.

Results

Overall, 51 patients were assessed, 33 females (64%) with mean age of 56±12 years. The presence of IPVD was observed in 31 patients (60%). Table 1 shows the clinical and laboratory parameters and Table 2 shows the endoscopic and ultrasound parameters. The average brain uptake was 2.9±2.6% in the group with IPVD and 3.8±1.2% in patients without IPVD (p<0.005).

Figure 1 shows abnormal scintigraphy (brain uptake = 15.7%) and Figure 2 shows normal scintigraphy (brain uptake = 1.8%).

When groups were compared, a higher percentage of women in the group with IPVD was observed (74.2% vs 50%), with p = 0.07. There were no statistically significant differences between groups regarding previous episodes of gastrointestinal bleeding or in relation to albumin (4.2±0.7 vs 4.1±0.7 g/dL), bilirubin (1.1±0.5 vs. 1.2±0.5 mg/dL), RNI (1.2±0.2 vs. 1.3±0.2), AST (37±18 vs 37±16 U/L) ALT (33±16 vs 38±21 U/L), and platelet values (100,000±51,000 vs. 88,000±36,000 per mm³).

When endoscopic parameters were evaluated, higher percentage of varices grades II and III in patients without IPVD was observed. Among ultrasound parameters, statistically significant differences were observed between groups when the splenic vein diameter was measured, with higher values for group without IPVD (0.9±0.3 in G1 vs 1.2±0.4 cm in G2, p = 0.029).

Discussion

To the best of our knowledge, this is the first study to evaluate the IPVD frequency in HSS patients by ⁹⁹mTc-MAA scintigraphy and its association with indirect portal hypertension parameters. In this study, IPVD frequency was 60% and its presence was associated to lower splenic vein diameter. This interesting result may reflect a protective mechanism of the pulmonary vascular system against portal hypertension.

In cirrhcots patients, the occurrence of IPVD ranged from 13 to 47% [16,17]. In a study with children with portal hypertension, Shabravi et al. found nearly twice the frequency of IPVD when ⁹⁹mTc-MAA scintigraphy data were compared to those using echocardiography [10]. Using transthoracic Doppler echocardiography...
small dilations in the pulmonary vasculature even before the sensitivity of 99mTc-MAA scintigraphy, which is able to identify sensitivity and specificity. This high frequency suggests greater and 99mTc-MAA scintigraphy showed conflicting results regarding aminotransferase; RNI – Ratio Normalized International; AST – alanine aminotransferase; ALT – alkaline phosphatase (UI/L) 116

Table 1. Clinical and laboratory parameters.

| Parameters          | Total   | G1       | G2       | p-value |
|---------------------|---------|----------|----------|---------|
| **Clinical**        |         |          |          |         |
| Age (years)         | 55.8±13.2  | 56.7±13.9 | 54.6±12.2 | 0.573   |
| Sex                 |          |          |          |         |
| Female              | 33 (64.7%) | 23 (74.2%) | 10 (50%)  | 0.078   |
| Male                | 18 (35.3%) | 08 (25.8%) | 10 (50%)  |          |
| **Gastrointestinal bleeding** |          |          |          |         |
| No                  | 30 (58.8%) | 20 (63.3%) | 10 (50%)  |          |
| Yes                 | 21 (41.2%) | 11 (36.7%) | 10 (50%)  | 0.35    |
| **Laboratory**      |         |          |          |         |
| Albumin (g/dL)      | 4.2±0.7  | 4.2±0.7  | 4.1±0.7  | 0.38    |
| Bilirubin (mg/dL)   | 1.1±0.5  | 1.1±0.5  | 1.2±0.5  | 0.13    |
| RNI (UI/L)          | 38.2±18.5 | 36.5±17.9 | 37.1±15.9 | 0.72    |
| AST (UI/L)          | 36.2±19.9 | 33.1±15.8 | 38.3±20.9 | 0.19    |
| ALP (UI/L)          | 92±44    | 100±51   | 88±36    | 0.27    |
| Platelets (x10^11 p/mm3) | 116±52 | 107±46.3  | 126±57.5 | 0.19    |
| γGT (UI/L)          | 120±82   | 96±67.6  | 141±105.2| 0.19    |
| RNI – Ratio Normalized International; AST – alanine aminotransferase; ALT – aspartate aminotransferase; γGT – γ-glutamil transferase. doi:10.1371/journal.pntd.0002881.t001

in patients with schistosomiasis already with gas exchange alterations (Da-Ao2>15 mmHg), Ferreira et al. found an IPVD frequency of 22% [8].

Studies comparing transthoracic Doppler echocardiography and 99mTc-MAA scintigraphy showed conflicting results regarding sensitivity and specificity. This high frequency suggests greater sensitivity of 99mTc-MAA scintigraphy, which is able to identify small dilations in the pulmonary vasculature even before the development of HPS [10,18]. Furthermore, this study was carried out in an University Hospital and all patients had esophageal varices, suggesting that more severe patients are examined, which may be one of the factors for the high IPVD frequency found. However, there are no studies assessing the importance of early IPVD diagnosis or the factors that leads to the development of HPS from the emergence of vascular dilatation in HSS.

In cirrhotic patients, it is well established that the presence of IPVD associated with hypoxemia is related to a higher MELD score [19,20] and a worse prognosis [4,21]. In a study carried out with patients without abnormal liver function Eldridge et al. showed the emergence of IPVD during the performance of physical exercises with spontaneous resolution during rest. In this group, the formation of vascular dilatation may be a defense mechanism to increased vascular pressure and blood flow in the pulmonary circulation [22]. In patients with schistosomiasis, the clinical relevance of the presence of IPVD is not well defined. In this study, no differences in the parameters that evaluated liver function among patients with and without IPVD were observed.

Aller et al showed that in cirrhotic males with IPVD, the serum levels of female sex hormones are higher than in patients without IPVD [23]. In patients with schistosomiasis, as there is no significant change in liver function, there should be no difference in the progesterone and estradiol levels in male patients compared to normal individuals. The high IPVD frequency in female patients found in this study suggests that these hormones may participate in the pathogenesis of the formation of this change, with vasodilatory effect, but further studies are needed to evaluate this association.

In patients with HSS, the obstruction to the hepatic blood flow caused by periportal fibrosis leads to increased pressure in the portal venous system [24]. The changes caused by portal hypertension are among the leading causes of morbidity and mortality in patients with schistosomiasis [25]. Formation of portal-systemic collateral circulation and increased portal and splenic vein diameter are the main changes occurring in the portal venous system of patients with schistosomiasis [1,26].

This study demonstrates that patients with schistosomiasis and IPVD had smaller splenic vein diameters, suggesting that vascular dilation would be a mechanism to reduce pressure in the portal territory. Moreover, the group with IPVD showed a greater proportion of patients with collateral circulation (64% vs 40%), lower average longitudinal spleen diameter (15.6 cm×16.5 cm) and high platelet levels (100×10^9 vs 88×10^9) although was not statistically significant. It was also found that the group with IPVD had a lower proportion of patients with varices of medium and development of HPS [10,18]. Furthermore, this study was carried out in an University Hospital and all patients had esophageal varices, suggesting that more severe patients are examined, which may be one of the factors for the high IPVD frequency found. However, there are no studies assessing the importance of early IPVD diagnosis or the factors that leads to the development of HPS from the emergence of vascular dilatation in HSS.

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Figure 1. Anormal scintigraphy. Brain uptake = 15.7%. doi:10.1371/journal.pntd.0002881.g001
large diameter, suggesting that this group presents lower portal pressure levels.

The number of patients included in this study may not have been sufficient to demonstrate the most significant differences in indirect markers of portal hypertension between groups with and without IPVD. Moreover, it is necessary to investigate whether these findings are also observed in individuals with portal hypertension of other etiologies. Our team is conducting another study evaluating the IPVD frequency in patients with chronic liver disease of mixed etiology. Further studies should be carried out in other regions and centers for comparison purposes.

Conclusion

In patients with HSS, the occurrence of IPVD evaluated by 99mTc-MAA scintigraphy was high and associated with lower splenic vein diameter, which can be a mechanism of vascular protection against portal hypertension. However, more studies are needed to determine the clinical significance of the early diagnosis and natural evolution of IPVD in this population.

Author Contributions

Conceived and designed the experiments: ASSdQ SCSB ALCD EPAL. Performed the experiments: ASSdQ SCSB ALCD LGM MSO. Analyzed the data: ASSdQ SCSB ALCD EPAL. Wrote the paper: ASSdQ SCSB ALCD EPAL.

References

1. Andrade ZA (2009) Schistosomiasis and liver fibrosis. Parasite Immunol 31: 636–643.
2. Health monitoring system. Acess in 31/05/2012. Available in http://portal.saude.gov.br/portal/saude/profissional/area.
3. Macêdo LG, Lopes EP, de Albuquerque MeF, Markman-Filho B, Veras FH, de Araújo AC, et al. (2010) Occurrence of hepatopulmonary syndrome in patients with cirrhosis who are candidates for liver transplantation. J Bras Pneumol 36: 432–440.
4. Fallon MB, Krowka MJ, Brown RS, Trotter JF, Zacks S et al. (2008) Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. Gastroenterology 135: 1168–1175.
5. Rodríguez de Araújo Souza M, Fischer de Toledo C, Borges DR (2000) Thrombocytopenia as a Predictor of Portal Hypertension in Schistosomiasis. Digestive Diseases and Sciences 45: 1964–1970.
6. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB, Committee EFFP-HVDPS (2004) Pulmonary-Hepatic vascular Disorders (PHD). Eur Respir J 24: 983–989.
7. Mandell MS (2007) Clinical controversies surrounding the diagnosis and treatment of hepatopulmonary syndrome. Minerva Anestiol 73: 347–355.
8. Ferreira ReC, Domingues AL, Markman Filho B, Veras FH, Batista LJ et al. (2009) Hepatopulmonary syndrome in patients with Schistosoma mansoni periportal fibrosis. Acta Trop 111: 119–124.
9. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB, Committee EFFP-HVDPS. Highlights of the ERS Task Force on pulmonary-hepatic vascular disorders (PHD). (2003) Journal of Hepatology 42: 924–927.
10. El-Shahrawi MH, Omar S, Wagedh S, Isu M, Okasha S et al. (2010) (99mTechnetium-macroaggregated albumin perfusion lung scan versus contrast enhanced echocardiography in the diagnosis of the hepatopulmonary syndrome in children with chronic liver disease. Eur J Gastroenterol Hepatol 22: 1006–1012.
11. Kalambski G, Tsiamos EV (2010). Lung perfusion scan is not superior to contrast-enhanced echocardiography for the diagnosis of the hepatopulmonary syndrome in chronic liver disease. Eur J Gastroenterol Hepatol 22: 1367–1380.
12. Macêdo LG, Lopes EP. (2009) Hepatopulmonary syndrome: an update Sao Paulo Med J 127:223–230.
13. Beppu K, Iookashi K, Koyanagi N, Nakayama S, Sakata H et al. (1981) Prediction of varical hemorrhage by esophageal endoscopy. Gastrointest Endosc 27: 213–218.
14. World Health Organization/TDR/SCH/ULTRASON (2000) Ultrasound in schistosomiasis. A practical guide to the standardized use of ultrasoundography for the assessment of schistosomiasis related morbidity.
15. Abrams G, Jaffe C, Hoffler P, Binder H, Fallon MB (1995) Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepato-pulmonary syndrome. Gastroenterology 109: 1283–1288.
16. Navie J (2003) Hepatopulmonary syndrome and portopulmonary hypertension. Swiss Med Wkly 133:163–169.
17. Whyte MK, Hughes JM, Peters AM, Usos W, Patel S et al. (1998) Analysis of intrapulmonary right to left shunt in the hepatopulmonary syndrome. J Hepatol 29:85–93.
18. Abbasouaan LS, Stoller JK (2000) The hepatopulmonary syndrome. Baillieres Best Pract Res Clin Gastroenterol 14: 1033–1040.
19. Sari S, Oguz D, Sucak T, Dalgic B, Atasever T (2012) Hepatopulmonary syndrome in children with cirrhotic and non-cirrhotic portal hypertension: a single-center experience. Dig Dis Sci 57:175–181.
20. Ferreira PP, Camara EJ, Paula RL, Zollinger CC, Cavalcanti AR et al. (2008) Prevalence of hepatopulmonary syndrome in patients with decompensated chronic liver disease and its impact on short-term survival Arq Gastroenterol 45: 34–57.
21. Egea H, Kasahara M, Inomata Y, Uemoto S, Asouma K et al. (1999) Long-term outcome of living related liver transplantation for patients with intrapulmonary shunting and strategy for complications. Transplantation 67: 712–717.
22. Eldridge MW, Dempsey JA, Haverkamp HC, Lovering AT, Hokanson JS (2004) Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. J Appl Physiol 97: 797–805.
23. Aller R, de Luis DA, Moreira V, Boixeda D, Moya JL et al. (2001) The effect of liver transplantation on circulating levels of estradiol and progesterone in male
patients: parallelism with hepatopulmonary syndrome and systemic hyperdynamic circulation improvement. J Endocrinol Invest 24: 503–509.

24. Vezozzo DC, Farias AQ, Cerri GG, Da Silva LC, Carrilho PJ (2006) Assessment of portal hemodynamics by Doppler ultrasound and of liver morphology in the hepatosplenic and hepatointestinal forms of schistosomiasis mansoni. Dig Dis Sci 51: 1413–1419.

25. Mudawi H, Ali Y, El Tahir M (2008) Prevalence of gastric varices and portal hypertensive gastropathy in patients with Symmers periportal fibrosis. Ann Saudi Med 28: 42–44.

26. Palikhe M, Xue H, Jha RK, Li YC, Yuan J et al. (2013) Changes in portal hemodynamics after TIPS in liver cirrhosis and portal hypertension. Scand J Gastroenterol 48:570–576.