Ultrasonographic assessment of splenic siderotic nodules in schistosomal patients with portal hypertension*

Avaliação ultra-sonográfica de nódulos sideróticos esplênicos em pacientes esquistossomóticos com hipertensão portal

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Abstract

OBJECTIVE: To evaluate ultrasound sensitivity and reproducibility as compared with magnetic resonance imaging as the gold standard in the detection of splenic siderotic nodules in schistosomal patients. MATERIALS AND METHODS: Initially, 21 patients with hepatosplenic schistosomiasis and diagnosed with splenic siderotic nodules by magnetic resonance imaging were ultrasonographically evaluated for determining the method sensitivity. In a second phase, the method reproducibility in the detection and quantification of siderotic nodules (A: 1–5 nodules; B: 6–20 nodules; C: > 20 nodules) was evaluated in 30 patients who were submitted to ultrasonography blindly and independently assessed by two observers. Interobserver agreement was measured by kappa statistics. RESULTS: Ultrasound sensitivity was 95.2% (95% confidence interval [77.3%; 99.2%]). Intermethod agreement in the detection of siderotic nodules was 96.7% (95% confidence interval [82.8%; 99.9%]). For classification of nodules according to their quantification, the kappa test demonstrated a statistically significant interobserver agreement (kappa = 0.67). CONCLUSION: Ultrasonography is highly sensitive and accurate in the assessment of splenic siderotic nodules in schistosomal patients.

Keywords: Schistosomiasis mansoni; Ultrasonography; Spleen – ultrasonography.

Resumo

OBJETIVO: Medir a sensibilidade e a reprodutibilidade da ultra-sonografia na detecção de nódulos sideróticos esplênicos em pacientes esquistossomóticos, tendo a ressonância magnética como padrão de referência. MATERIAIS E MÉTODOS: Na primeira fase do trabalho, 21 pacientes portadores de esquistossomose na forma hepatoesplênica com diagnóstico de nódulos sideróticos à ressonância magnética foram submetidos a avaliação ultra-sonográfica para a determinação da sensibilidade do método. Na segunda fase, com o objetivo de avaliar a reprodutibilidade da ultra-sonografia na detecção e na quantificação de nódulos sideróticos (A: 1–5 nódulos; B: 6–20 nódulos; C: mais de 20 nódulos), outros 30 pacientes esquistossomóticos foram submetidos a avaliação ultra-sonográfica de forma cega e independente por dois observadores. A reprodutibilidade foi medida por meio da concordância entre os observadores e do teste kappa. RESULTADOS: A sensibilidade da ultra-sonografia foi de 95,2% (intervalo de confiança a 95% [77,3%; 99,2%]). A concordância entre ultra-sonografia e ressonância magnética para a detecção de nódulos sideróticos foi de 96,7% (intervalo de confiança a 95% [82,8%; 99,9%]). Para a classificação dos nódulos conforme a sua quantificação, o índice kappa demonstrou concordância interobservador substancial (kappa = 0,67). CONCLUSÃO: A ultra-sonografia é um método que apresenta elevada sensibilidade e boa precisão para a avaliação de nódulos sideróticos esplênicos.

Unitermos: Esquistossomose; Ultra-sonografia; Baço – ultra-sonografia.

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INTRODUCTION

Schistosomiasis still remains as a relevant problem of public health both in Brazil and worldwide, where it is estimated that, respectively, 18 and 200 million persons are infected[1-3]. Ultrasonography (US) is the method most frequently utilized for assessing schistosomal patients in the
hepatosplenic phase of the disease character- 
ized by portal hypertension secondary to the development of perportal fibrosis\(^4\-6\).

Siderotic nodules, or Gamma-Gandy bodies, consist in small fibrotic nodules impregnated with hemosiderin, resulting from focal micro-hemorrhages in the splenic parenchyma caused by vascular congestion in this organ. Portal hypertension is the most frequent cause of splenic siderotic nodules\(^7\).

Gamma-Gandy bodies may be evaluated by different imaging methods\(^8\), but presently magnetic resonance imaging (MRI) especially with gradient-echo sequences is considered as the method of choice in the detection of these nodules\(^9\-10\). The US value in the assessment of Gamma-Gandy bodies has been discussed in the literature with controversial results and sensitivity ranging between 12% and 70.6%\(^11\).

As regards diagnostic tests, a decisive parameter to be taken into consideration is the method accuracy that can be evaluated by means of its reproducibility. No study is available in the current literature evaluating the US reproducibility based on the measurement of interobserver agreement for detection of splenic siderotic nodules.

The present study was aimed at measuring the sensitivity and reproducibility of US in the detection of splenic siderotic nodules in comparison with magnetic resonance imaging as standard method.

**MATERIALS AND METHODS**

**Patients’ selection**

In the first phase of the present study, 20 patients with hepatosplenic schistosomiasis (11 men and nine women in the age range between 23 and 87 years, mean age = 44 years), diagnosed with siderotic nodules at MRI and submitted to ultrasonographic evaluation in a term of less than three months for determining the sensitivity of US in the detection of splenic siderotic nodules in comparison with magnetic resonance imaging as standard method.

Ultrasonography studies were performed on an EnVisor\(^\text{TM}\) (Philips Medical Systems; Bothell, WA, USA) equipment coupled with a convex, multi-frequency transducer.

The diagnosis was considered as positive for siderotic nodules in the presence of dispersed, hyperechogenic, parenchymal foci non-attributable to thickened vessels walls in the spleen (Figure 2). Siderotic nodules identified were classified according to methodology already proposed\(^12\), as follows:

- Category A: a transverse section of the spleen demonstrating < 5 nodules (focal);
- category B: a transverse section of the spleen demonstrating 6-20 nodules (scattered);
- category C: a transverse section of the spleen demonstrating > 20 nodules (diffuse).

**Figure 1.** Upper abdominal MRI study: T1- (a) and T2-weighted (b) gradient-echo sequences showing foci with remarkable low-signal intensity on the splenic parenchyma compatible with siderotic nodules (arrows).
Ultrasonographic assessment of splenic siderotic nodules

The evaluation of the US reproducibility in determining the presence of siderotic nodules in the 30 patients included in the present study demonstrated an interobserver agreement of 96.7% (confidence interval at 95% [82.8%; 99.9%]). The reproducibility of the classification of siderotic nodules into categories according to their quantity, demonstrated a substantial interobserver agreement (kappa = 0.672; confidence interval at 95% [0.374; 0.970]).

DISCUSSION

US is considered as the method of choice in the evaluation of schistosomal patients, considering its wide availability, excellent cost-benefit ratio, and non-invasiveness. Sonographic alterations detected in these patients have already been described and currently are widely utilized both for evaluating the hepatic involvement, determining the level of portal hypertension and characterizing splenic siderotic nodules. However, for establishing the validity of a diagnostic test, it is important to define, besides its efficacy, its accuracy, which can be determined by calculating the method reproducibility. The present study has been driven particularly by the absence, in the medical literature, of a systematic evaluation of the US reproducibility by means of the measurement of interobserver agreement as regards the detection of splenic siderotic nodules.

Siderotic nodules, or Gamma-Gandy bodies, were firstly described by Marini, in 1902, but this entity became actually known with the studies developed in 1905 and 1921 by Charles Gandy and Carlo Gamna, giving rise to the eponym. Siderotic nodules consist in small fibrotic nodules impregnated with hemosiderin and, in some cases with calcifications resulting from focal micro-hemorrhages in the splenic parenchyma, generally related to congestive splenomegaly (Figures 3 and 4). Most rarely, siderotic nodules may be found in other tissues such as thymus, lymphonodi, liver, heart, and in conditions such as paroxysmal nocturnal hemoglobinuria, leukemia and lymphoma. However, portal hypertension is the most frequent cause of these nodules, which are present in about 9% to 12% of patients with portal hypertension for causes unrelated to schistosomiasis.

**Statistical analysis**

The interobserver agreement was measured by means of kappa index, an useful test for classifying the variability in the interpretation of different data sets including categorical variables. Kappa indices were classified as follows: non-significant (0.0–0.2), median (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost-perfect (0.81–1.00).

**RESULTS**

Twenty of the 21 patients with siderotic nodules detected by MRI were correctly evaluated by US, whereas in only one patient ultrasound could not detect these nodules, giving the method a sensitivity of 95.2% (confidence interval at 95% [77.3%; 99.2%]).

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The relevance of detecting the presence of splenic siderotic nodules by means of imaging methods is related to the fact that these nodules represent a morphological evidence of a long lasting portal hypertension process\(^{20}\).

Currently the relevant role of MRI as a reference method in the detection of siderotic nodules is a consensus in the literature\(^{8–10,20–23}\). MRI is extremely sensitive to paramagnetic contrast agents; hemoglobin products (for example, hemosiderin) have a paramagnetic effect, being easily detected on RM images (especially the high field ones), were they appear like low-signal intensity nodules or absent signal on spin-echo and especially gradient-echo T1- and T2-weighted images\(^{8,9,20}\) (Figure 1). These nodules also can be evaluated by other imaging methods such as computed tomography (CT) and US. On US images, the nodules appear as small, punctate hyperechogenic foci sparsely scattered in the splenic parenchyma, with or without posterior acoustic shadowing, non-attributable to small vessels walls\(^{7}\) (Figure 2).

The incidence of these nodules initially described in the literature for schistosomal patients in the hepatosplenic phase, was of \(7\%\) in studies utilizing US as imaging method\(^{14}\). Most recently, studies utilizing MRI have found a much higher incidence of siderotic nodules (84.2\%) in schistosomal patients\(^{21}\). In the present study, the frequency of detection of siderotic nodules by US and MRI in patients with hepatosplenic schistosomiasis was also very high, ranging between 96.6\% and 100\%.

Ultrasonography sensitivity in the detection of siderotic nodules also has been discussed. Differently from previous studies developed in the eighties, reporting sensitivities between 10.5\% and 25\%\(^{9,10}\), the current literature describes a high diagnostic accuracy for this method, with 70.6\% sensitivity, 78.9\% specificity, and 85.7\% positive predictive value\(^{11}\). The results of the present study surpassed these latter, with 95.2\% sensitivity. This discrepancy in relation to the US frequency and sensitivity in detecting siderotic nodules can be attributed to the utilization of observers specifically trained for researching these nodules, and, also, to the technological developments of US systems over the last two decades, with an expressive improvement in their images resolution.

Apparently, in cirrhotic patients, the presence and number of siderotic nodules are associated with their level of portal hypertension\(^{20}\). The quantification of these nodules and their classification into categories according to the number of nodules found had been already proposed for the liver\(^{12}\), but had not been utilized for the spleen yet. The present study found a high interobserver agreement as to the overall presence or absence of siderotic nodules (96.7\%). Regarding the US reproducibility for the quantification and classification of siderotic nodules into categories, the kappa index showed a substantial interobserver agreement (0.67). Additional studies are required for determining the significance of this quantification and its actual correlation with the level of portal hypertension.

In addition, in the present study, a tendency towards a higher interobserver agreement was observed in relation to patients with a higher number of siderotic nodules (category C). In the patients with lower number of siderotic nodules (especially in those of category A), the difficulty found by the observers was the differentiation between true nodules and small vessels walls; color Doppler US may be useful in this differentiation. In the present study, however, color Doppler US could not be utilized, considering that this previously unforeseen difficulty occurred only with some patients evaluated late in the development of the study.

Amongst the differential diagnoses for splenic siderotic nodules observed at US, tuberculosis calcified granulomas should be considered. These granulomas tend to be larger and more hyperechogenic than siderotic nodules, besides presenting an evident acoustic shadowing, a feature that is not present in the case of non-calcified siderotic nodules\(^{9}\), which represented the majority in the present study. Additionally, because of the paramagnetic effect of hemosiderin products, siderotic nodules are clearly visualized on T1- and T2-weighted images as small foci of low-intensity or absent signal and without contrast-enhancement after intravenous gadolinium injection\(^{9,10}\). Conversely, non-calcified tuberculotic nodules tend to present a variable signal on T1- and T2-weighted images, and most frequently with hyper-intense signal and ring-shaped contrast-enhancement after gadolinium injection\(^{24}\). Calcified siderotic nodules may not be distinguishable from different types of calcified granulomas, like those resulting from tuberculosis and histoplasmosis\(^{9}\).

Amongst the limitations of the present study, it is important to note the restricted number of patients included in the sample, as well as the absence of a control group which would allow the addition of other useful information (for example, specificity, positive and negative predictive values) for determining the US diagnostic accuracy in the detection of these nodules. Certainly, MRI cost and availability represent a limiting factor for the further expansion of the sample. Notwithstanding, it is important to note that the group of patients included in the present study reflects the reality of our institution, as it may be evidenced by other studies in this same research line\(^{25,26}\).

Considering the lack of previous experiments, the quantitative classification of splenic siderotic nodules was adapted from a classification proposed for hepatic siderotic nodules in cirrhotic patients\(^{11}\), and that was not previously validated in schistosomal patients. Another type of classification could demonstrate results different from the ones in the present study.

Finally, just as demonstrated by other authors\(^{4}\), the present study demonstrated that ultrasonography, besides being a low-cost, non-invasive and widely available imaging method, is highly sensitive and reproducible in the evaluation of splenic siderotic nodules in patients affected by schistosomal portal hypertension.

REFERENCES

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