
Abdominal ultrasound (US) is considered a simple, safe and inexpensive imaging technique in the evaluation of schistosomal liver involvement and is often used as the surrogate for the gold-standard in diagnosing liver fibrosis (LF); none has used magnetic resonance (MR). The aim of this study was to evaluate schistosomal LF using these three methods. Fourteen patients with hepatosplenic schistosomiasis admitted to hospital for surgical treatment of variceal bleeding were investigated. They were submitted to upper digestive endoscopy, US, MR and wedge liver biopsy. The World Health Organization protocol for US in schistosomiasis was used. Hepatic fibrosis was classified as absent, slight, moderate or intense. Histology and MR confirmed Symmers’ fibrosis in all cases. US failed to detect it in one patient. Moderate agreement was found comparing US to MR; poor agreement was found when US or MR were compared to histology. Re-classifying LF as only slight or intense created moderate agreement between imaging techniques and histology. Histomorphometry did not separate slight from intense LF. Two patients with advanced hepatosplenic schistosomiasis presented slight LF. Our data suggest that the presence of the characteristic periportal fibrosis, diagnosed by US, MR or histology, associated with a sign of portal hypertension, defines the severity of the disease. We conclude that imaging techniques are reliable to define the presence of LF but fail in grading its intensity.

Key words: schistosomiasis - ultrasound - magnetic resonance - liver fibrosis - Symmers’ fibrosis - splenectomy - portal hypertension

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PATIENTS, MATERIALS AND METHODS

Patients - The study was approved by the Ethical Board of the Federal University of Minas Gerais, Brazil.
All study subjects signed an informed consent for participation. Fourteen patients (10 males) referred to the Tropical Diseases Outpatient Clinic with a diagnosis of hepatosplenic schistosomiasis, portal hypertension and indication for surgical intervention (splenectomy and/or suturing of oesophago-gastric varices) were selected for this study. Schistosomiasis was defined by microscopic evidence of active infection (positive parasitological stool examination or eggs in rectal biopsy) and a history of contact with stream waters of an endemic area. Patients included in the study did not have other causes of chronic liver disease, such as cirrhosis, congestive heart failure or toxic or viral hepatitis. Age ranged from 20-57 years (39 ± 10.4). Baseline characteristics are presented in Table I.

Methods - Outpatient assessment included clinical examination, abdominal US, upper digestive endoscopy, serum markers of autoimmune hepatitis, hepatitis B and C serology, blood cell count and liver function evaluation (serum albumin and prothrombin time). Seventeen patients fulfilled the criteria for inclusion, but three were excluded because wedge liver biopsy was not available or because of sclerosing cholangitis (Fig. 1).

US examination of the abdomen was performed using a real-time ALOKA SSD device 1700 (Japan) with electronic convex 3.5 MHz transducer, according to the WHO protocol for US assessment of schistosomiasis-related morbidity (Niamey Working Group 1996). US hepatic fibrosis was classified as absent (pattern A), slight (B, C, D and Dc), moderate (E and Ec) or intense (F). The presence of collateral vessels and the spleen length were evaluated. MR was obtained using a GE 1.5 T Sigma unit (Milwaukee, USA). Axial and coronal 7-mm-thick slices were performed in T1 and T2-weighted sequences, before and after gadopentetate dimeglumine (Gd-DTPA) administration. MR analysis was guided by an adaptation of the WHO protocol for US. US and MR were blindly performed (Fig. 2). Radiologists and pathologists knew that all patients had schistosomiasis, but they were not informed of the clinical form of the disease.

Radiology was the specialty of both observers. The US examiner had seven years of experience in radiology; he was trained to use the WHO protocol for US-related morbidity in schistosomiasis. The MR examiner had 10 years of experience in radiology. One observer viewed the MR and other the US images. The inter-observer agreement for US has been reported to be moderate (kappa 0.45) (Doehringer et al. 1992). For MR the intra and inter-observer agreement has been shown to be substantial (kappa 0.65 and 0.66, respectively) (Bezerra et al. 2007).

Wedge liver biopsy fragments of ~3 cm³ were obtained from the left liver lobe during splenectomy, fixed

Advanced hepatosplenic schistosomiasis with portal hypertension (n = 17)

Excluded (n = 3)

No wedge liver biopsy (n = 2)
Sclerosing cholangitis (n = 1)

Included (n = 14)

Upper endoscopy, ultrasound, magnetic resonance and wedge liver biopsy

Histology and histomorphometry

Fig. 1: study’s flow chart.

<table>
<thead>
<tr>
<th>Characteristics of subjects (n = 14)</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years ± SD</td>
<td>39 ± 10.4</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>(20-57)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
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<tr>
<td>Skin color</td>
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</tr>
<tr>
<td>White</td>
<td>4</td>
</tr>
<tr>
<td>Non white</td>
<td>10</td>
</tr>
<tr>
<td>Exposed to stream waters</td>
<td>14</td>
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<tr>
<td>Upper digestive bleeding</td>
<td>12</td>
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<tr>
<td>Positive parasitological stool exam</td>
<td>2</td>
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<tr>
<td>Previous treatment for Schistosoma</td>
<td>8</td>
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<tr>
<td>mansoni</td>
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<tr>
<td>Hemograma</td>
<td></td>
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<tr>
<td>Leukopenia</td>
<td>11</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
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<tr>
<td>Palpable liver</td>
<td>9</td>
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<tr>
<td>Palpable spleen b</td>
<td>11</td>
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<tr>
<td>Previous splenectomy b</td>
<td>2</td>
</tr>
</tbody>
</table>

a: anaemia: Hb < 12g% women and < 14g% men; thrombocytopenia: platelets < 150.000 mm³; leukopenia: global leukocytes < 4.300 cels/mm³; b: two were submitted to previous splenectomy and one was obese, two subjects had only palpable spleen.
in 10% formalin and embedded in paraffin (Fig. 3). The section preparations were stained with hematoxylin and eosin (H&E) and were examined under light microscopy. Randomly sampled 5-μm-thick liver histological sections stained with picrosirius red for interstitial collagen were examined by semiautomatic morphometry using the LEICA QWIN-3.1 (Microsystem Imagina Solutions LTD, Cambridge, UK) (Fig. 4). For morphometric measurements a total sectional area of 4,296,920 m² per patient was evaluated. The sectional area of the red-stained fibrous tissue was directly measured and calculated as a percentage of the total area examined, as previously described (Barbosa 2001, Coutinho et al. 2003).

**RESULTS**

All patients had oesophageal varices confirmed by endoscopy and 12 reported some form of previous digestive bleeding. Only four patients underwent sclerotherapy of oesophageal varices. Two patients excreting *Schistosoma mansoni* eggs were treated with praziquantel.

In 13 out of 14 (92.8%) patients, US showed the characteristic features of schistosomal liver fibrosis, whereas MR identified periportal thickening in all 14.

Patients with hepatosplenic schistosomiasis are shown in Fig. 5. Symmers’ fibrosis was confirmed by histology. The white clay pipe-stem aspect was present in all cases, with variable degrees of septal fibrosis maintaining the acinar architecture of the hepatic parenchyma. Periovular granulomas were rare, small, fibrotic and sometimes with calcified ova.

During splenectomy, the liver surface presented a wide range of patterns (Fig. 6). The surface varied from smooth to pseudo-nodular with macroscopic whitish bands. Liver wedges also varied from sharp to blunt and consistency varied from soft to hard.

US, MR and histology classified hepatic fibrosis as moderate in four patients (28.5%; patients 3, 4, 6 and 14). In six patients (42.8%) the difference in the intensity of fibrosis diagnosed by the different methods was
of one degree, e.g., from moderate to intense (patients 1, 2, 9, 10, 11 and 12). The three methods completely disagreed in four patients (28.5%; patients 5, 7, 8 and 13). These results are summarised in Table II. Agreement between imaging methods, as evaluated by kappa index, was 0.41 (moderate); after re-grouping grades absent and slight together (labelled slight) and grades moderate and intense together (labelled intense), substantial concordance was observed (kappa = 0.63).

Agreement between US and histology was poor (kappa = 0.06) and remained so even after re-grouping into slight and intense (kappa = -0.17). Similar results were observed comparing MR to histology. Excluding one patient (patient 7, Table II) who presented absent fibrosis in US and moderate fibrosis in MR, the agreement was moderate between imaging techniques and histology (kappa = 0.41). If this patient was kept in the comparison, the obtained agreement was poor (kappa = 0.10).

There was no agreement (kappa < 0) between histomorphometric classification of fibrosis and the subjective histological classification.

No correlation was observed between spleen size or upper digestive bleeding and the intensity of LF.

**DISCUSSION**

Histology and MR confirmed Symmers’ fibrosis in all cases; US failed to identify one patient. Imaging techniques presented moderate agreement with histology to rank LF. Histomorphometry did not agree with the histological classification of fibrosis. We also observed two patients with advanced hepatosplenic schistosomiasis with light LF.

Surgical wedge liver biopsy is considered the gold-standard procedure for diagnosing Symmers’ fibrosis. In our study, MR identified LF with the same precision as histology. A marked divergence, though, occurred during classification of fibrosis intensity. Other studies using MR contained case reports or series of cases and they did not include liver biopsy to confirm the diagnosis and intensity of Symmers’ fibrosis. However, using US, Homeida et al. (1988b) found results comparable to ours: the diagnosis of LF by US coincided with histology, but they presented poor agreement on fibrosis intensity.

Other studies used US to diagnosis the presence and grade the intensity of LF, but liver biopsy was only employed to confirm Symmers’ fibrosis and to exclude other liver diseases (Abdel-Wahab et al. 1978, 1989, 1992, Cerri et al. 1984, Homeida et al. 1988a, Pinto-Silva et al. 1994).

In one of our patients, US failed to diagnosis LF. This deficiency has been previously described by Abdel-Wahab et al. (1989). Of their 18 patients with histological diagnosis of Symmers’ fibrosis, two did not present US evidence of portal thickening. It is also important to comment on one patient with sclerosing cholangitis excluded from our study: US images were indistinguishable from what is seen in patients with Symmers’ fibrosis.

Needle liver biopsy frequently overlooks portal fibrosis because it retrieves insufficient and fragmentated tissue samples with a small number of portal tracts (Bogliolo 1957b). Taking this into consideration, our study was designed to obtain a surgical biopsy of the liver during splenectomy. Some authors criticise the wedge liver biopsy because fragments come from the periphery of the organ and fibrosis is not expected to be uniformly distributed (Brandt et al. 2002). Nevertheless, Dusek et al. (1965) states that a large enough specimen for histological assessment is obtainable only by surgical wedge biopsy and that the specimens are often sufficient to make an accurate diagnosis. In our opinion, the fragments obtained in our study (~3 cm²) were large enough to permit a definitive diagnosis of Symmers’ fibrosis.

Abdel-Wahab et al. (1992) and Richter et al. (1992) found that increases in portal and splenic vein diameters were significantly correlated with the degree of hepatic portal fibrosis and the frequency of bleeding from endoscopically proven oesophageal varices. Here, we found no correlation between spleen size or a history of oesophageal bleeding and LF intensity. Interestingly, Andrade and Bina (1983), describing an autopsy series of 232 cadavers, stated that they found no correlation between the intensity of LF and evidence of portal hypertension and that, in fact, the latter resulted from intra-hepatic vessel obstruction rather than from LF (Prata & Andrade 1963).

Histomorphometry is a method used to measure LF as a percentage of the hepatic tissue. No correlation between histological findings and morphometric measurements was observed in the present investigation. The reason for this is not clear, but a few points may be noted: (i) the usual histological examination by a pathologist is subjective and therefore difficult to evaluate (for exam-
ple, the classification of the intensity of fibrosis in hepatitis C is also subjective and a significant error among different examiners has been reported (de Paula Farah et al. 2007) and (ii) LF is not homogeneously dispersed in the liver and even in the same fragment, fibrosis may be unevenly distributed. The same results have been described by others (Domingues 1998, Brandt et al. 2002).

Computed tomography (CT) has been used in schistosomiasis mansoni, revealing the presence of hypodense areas in the portal tracts, enhanced after contrast injection (Patel et al. 1993, Willemsen et al. 1995). Similar tomographic aspects have been reported for other diseases, such as Kaposi’s sarcoma, sarcoïdosis and liver alterations post-chemotherapy. To our


TABLE II
Liver fibrosis and spleen size of 14 patients with advanced hepatosplenic schistosomiasis evaluated by physical examination, ultrasound (US), magnetic resonance (MR) and histology, Belo Horizonte, Minas Gerais, Brazil 2006-2007

<table>
<thead>
<tr>
<th>Subject</th>
<th>US</th>
<th>WHO pattern</th>
<th>MR</th>
<th>WHO pattern</th>
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<th>Physical examination</th>
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<td>M</td>
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<td>213</td>
<td>200</td>
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World Health Organization (WHO) patterns: A: absent; I: intense (F); L: slight (B, C, D, Dc); M: moderate (E, Ec) (Fig.2). Asterisk means splenectomized.

knowledge, there are no studies using positron emission tomography CT in hepatosplenic schistosomiasis. Non-invasive markers have also been used to predict the presence and degree of LF in hepatic diseases such as hepatitis C, cirrhosis and schistosomiasis (Stone 2000, Guangjin et al. 2002, Afdhal & Nunes 2004, Grigorescu 2006).

It is worth mentioning that MR reproduces the pathological findings of Symmers’ fibrosis more clearly than US does and is naturally less invasive and time-consuming than histology. The MR images are similar to those described by a pathologist when the liver is transversally cut during autopsy. Also, its superiority in the identification of portal vessels, portal vein thrombosis and collaterals should not be neglected (Bezerra et al. 2007). This information may help physicians plan in advance the surgical procedure that best suits their patients. On the other hand, MR is expensive. Due to its clear advantages, however, we believe it will be used more frequently in the near future.

Patients with hepatosplenic schistosomiasis in need of surgical intervention are those with severe portal hypertension, oesophageal varices and hypersplenism (thrombocytopenia, leukopenia and anaemia) (Petroianu 1983, 2003). It has been assumed that such patients would accordingly have intense periportal fibrosis, but here, we observed two patients with slight fibrosis diagnosed by histology presenting the severest clinical form of hepatosplenic schistosomiasis (huge spleens and massive variceal bleeding). Therefore, portal hypertension was probably caused by intrahepatic sinusoidal obstruction rather than periportal fibrosis.

In summary, LF intensity is not a definite surrogate marker of morbidity. Our data suggest that the intensity of LF evaluated by imaging techniques or histology does not relate to the severity of portal hypertension. The characteristic periportal fibrosis (diagnosed by US, MR or histology) associated with evidence of portal hypertension (large spleen, oesophageal varices and collateral vessels) should be sufficient to define disease severity and indicate surgical intervention, as necessary. We conclude that imaging techniques are reliable to define the presence of LF but fail in grading its intensity.

REFERENCES
Abdel-Wahab MF, Esmat G, Milad M, Abdel-Razek S, Strickland GT


