Hereditary-hemorrhagic telangiectasia: One-step magnetic resonance examination in evaluation of liver involvement

L. Milot, I. Kamaoui, G. Gautier, F. Pilleul

Service de radiologie digestive, hôpital Édouard-Herriot, pavillon GHN, place d'Arsonval, 69003 Lyon, France

Available online 30 August 2008

Summary

Purpose. — To describe the magnetic resonance imaging (MRI) features of hepatic involvement in hereditary-hemorrhagic telangiectasia (HHT) and to determine the interobserver agreement for all of them.

Patients and methods. — Twenty-three consecutive patients (including 17 women, mean age: 55 years) with HHT, according to the Curaçao criteria, underwent prospective MRI of the liver, including parenchymal, angiographic and biliary sequences, in one step. The scans were analyzed to determine the presence of vascular, biliary and parenchymal abnormalities (Mann–Whitney U test, χ²). The diameters of the hepatic vessels in the 23 patients were compared with those of 23 subjects with no signs of HHT or vascular or liver disease.

Results. — MRI of the liver was abnormal in 21 patients with suspected HHT (91%). Vascular abnormalities were found in 21 patients (91%), consisting of marked dilatation of the hepatic artery (N = 14), intrahepatic telangiectases (N = 21), arteriosystemic venous shunting (N = 19), arterioportal shunting (N = 11) and aneurysms of the hepatic artery (N = 3). Regenerative nodular hyperplasia was identified in 17 patients (74%) and ischemic cholangitis in nine (39%). No such lesions were found in the controls. The diameter of the hepatic artery proper was greater in patients with HHT than in the controls: 8.69 ± 1.63 mm versus 5.17 ± 0.44 mm, respectively (P < 0.05). Good interobserver agreement was found with parenchymal and vascular abnormalities (0.62) and moderate interobserver agreement (0.42) with biliary abnormalities.
Conclusion. — One-step MRI of the liver appears to be an excellent tool for the evaluation of liver involvement in HHT, revealing vascular abnormalities, telangiectases, arteriovenous shunting, focal-liver lesions and ischemic cholangitis.

© 2008 Elsevier Masson SAS. All rights reserved.

Résumé

Objectif. — Évaluer l’apport de l’imagerie par résonance magnétique (IRM) dans la détection des anomalies hépatiques de la télangiectasie hémorragique héréditaire (THH) et déterminer la concordance interobservateur des différents signes.

Patients et méthodes. — Vingt-trois patients consécutifs (17 femmes, d’âge moyen : 55 ans), suspects d’atteinte de la THH selon les critères de Curacao, ont été explorés par une IRM hépatique. L’exploration a combiné à la fois des séquences morphologiques, angiographiques et cholangiographiques. Les résultats ont été analysés par deux radiologues expérimentés qui ont recherché des anomalies vasculaires, parenchymateuses et biliaires. Le diamètre des vaisseaux hépatiques de ces 23 patients a été comparé au diamètre des vaisseaux hépatiques chez 23 sujets témoins sans maladie vasculaire ou hépatique.

Résultats. — L’IRM du foie était anormale chez 21 patients suspects de THH (91 %). Les anomalies vasculaires étaient présentes chez les 21 patients (91 %) et incluaient une dilatation de l’artère hépatique (n = 14), des télangiectasies intrahépatiques (n = 21), des fistules artério-veineuses (n = 19), des fistules artéioportes (n = 11), des anévrismes de l’artère hépatique (n = 3). Une hyperplasie nodulaire régénérative a été mise en évidence chez 17 patients (74 %) et une cholangite ischémique chez neuf patients (39 %). Ces anomalies décrites n’ont pas été trouvées chez les témoins. Le diamètre de l’artère hépatique était augmenté chez les patients atteints de THH par rapport aux sujets témoins et mesurait respectivement 8,69 ± 1,63 mm versus 5,17 ± 0,44 mm (p < 0,05). La concordance interobservateur des anomalies parenchymateuses et vasculaires était bonne et variait de 0,62 à 0,86. Celle des anomalies biliaires était modérée (0,42).

Conclusion. — L’IRM hépatique est un moyen d’imagerie utile dans l’évaluation de l’atteinte hépatique au cours des THH, permettant de mettre en évidence les anomalies vasculaires, parenchymateuses et biliaires.

© 2008 Elsevier Masson SAS. All rights reserved.
Hereditary hemorrhagic telangiectasia

as ultrasound examination or a CT scan. Clinical signs of liver dysfunction were identified (N = 8), including hepatoujugular reflux, hepatomegaly and pulsatile liver. Abnormal liver-function tests showed moderate-to-severe cholestasis (N = 8), with gamma-glutamyl transferase (GGT) and alkaline phosphatase levels more than two times the upper limit of normal. Signs of heart failure were found in five patients. The second group comprised 23 patients [11 women and 12 men, mean age 53.1 years (range: 21 to 72 years)] who had undergone MRI of the liver as potential liver donors and fulfilled none of the criteria for HHT or vascular or hepatic disorders.

MR imaging

All MRI studies were performed at 1.5 T with a Symphony MR imaging unit (Siemens Medical Systems, Erlangen, Germany) and a phased-array body coil. MRI examinations were performed according to the following protocol: transverse in-phase and out-of-phase modes; T1-weighted breath-hold spoiled gradient-echo sequences of the upper abdomen (repetition time (TR)/time echo (TE) 167/2.38, 4.76 ms; flip angle, 70; section thickness, 8 mm; 10% intersection gap; matrix size, 111 × 156); transverse double-echo T2-weighted fat-suppressed turbo spin-echo sequence (TR/TE, 156 × 8 ms; section thickness, 8 mm; 10% intersection gap; matrix size, 242 × 382); transverse T1-weighted breath-hold spoiled gradient-echo sequences (TR/TE, 183/1 ms; section thickness, 7 mm; matrix size, 176 × 512); coronal and coronal–oblique rapid acquisition with relaxation enhancement (TR/TE, 2390/1 ms; section thickness, 20 mm; matrix size, 242 × 512). The scan time for all sequences was less than 25 s to facilitate breath holding during acquisition, except for the transverse double-echo T1-weighted fat-suppressed turbo spin-echo sequence, which is a triggering sequence.

MRA was performed with a dual-phase protocol to visualize the arteriovenous-liver vasculature. We used a 3-D spoiled gradient-echo sequence with intermittent fat-saturation pulse in the coronal plane. Imaging parameters were: TR/TE 5.2/2 ms; 25° flip angle; 192 × 512 matrix; 400-mm mean field of view; 100-mm slab thickness; 64 partitions; 1.79-mm slice thickness and 25-second scan time for arterial and portal phases. Gadopentate dimeglumine (0.2 mmol/kg body weight) was intravenously administered using a power injector and was immediately followed by 20 mL of normal saline solution. The imaging protocol was completed with one continuous data-acquisition (venous-phase) scan, with a 12-second delay between two measurements. Before MRA acquisition, an initial test bolus of 2 mL of gadopentate dimeglumine was first administered to determine the subject’s circulation time to the vessel region of interest. An axial turbo fast low-angle shot was performed to acquire one image through the aorta at the level of the celiac trunk every 2 s for 60 s. The aorta image with maximum opacification was used to determine the time to peak opacification, which was also considered the patient’s circulation time and determined the optimal timing of the bolus sequence for the arterial-phase acquisition. The MR angiograms were postprocessed with a series of maximum-intensity projection (MIP) images and/or volume rendering technique (VRT) for texture artifact created by use of the entire acquired volume (Leonardo, software version 1; Siemens Medical Systems).

Image interpretation

All MRI scans were analyzed at a dedicated workstation by two experienced abdominal radiologists (GG, FP) who were blind to the clinical features. These observers first evaluated all the images independently. All evaluations were categorized and documented using standardized datasheets. For both the patients with HHT and the control group, the radiologists evaluated the presence of parenchymal lesions. Round, highly-enhanced lesions with high-signal intensities on T1-weighted sequences and a diameter less than 10 mm, seen in the liver with a predominantly peripheral arrangement, were considered parenchymal-hepatic telangiectases [20]. Regenerative nodular hyperplasia (RNH) was suspected in the case of a homogeneous lesion on T1- and T2-weighted sequences with no capsule and contrast enhancement in the arterial phase and homogeneity in the portal phase, with or without late enhancement of the central component [21]. The radiologists also evaluated biliary involvement. In the magnetic resonance cholangiopancreatography sequences, ischemic cholangitis was defined as an irregular biliary duct with strictures and upstream dilatation in the peripheral intrahepatic-biliary tract, with a diffuse or segmental distribution or ‘‘pruned tree’’ appearance [22]. Vessel involvement and the presence and type of shunts were also evaluated. On MRA sequences, arterial dilatation (a common hepatic artery greater than 7 mm in diameter) and tortuosity were evaluated. Anatomical variations in the hepatic arteries were evaluated in accordance with Michels’ classification [23]. Irregular fusiform or saccomform enlargements in the splanchnic arteries of greater than 10 mm were considered splanchnic aneurysms.

Three types of intrahepatic shunts between the major vessels of the liver are possible [5, 15, 24]: arterioporal (hepatic artery to portal vein); arteriosystemic (hepatic artery to hepatic vein) and portosystemic venous (portal vein to hepatic or systemic veins). Early and prolonged enhancement of the portal vein during the arterial phase was considered an indirect sign of the presence of arterioporal shunt [24]. Opacification of the hepatic veins during the arterial phase was considered an indirect sign of the presence of hepatic-arteriosystemic venous shunt. Evidence of dilated portal veins communicating with the large systemic or hepatic vein during the portal-venous phase was considered a sign of intrahepatic-portosystemic venous shunt. After this first step, consensus was achieved between the two readers.

Statistical analyses

Vascular measurement

Because we assume that the two populations are independent and population distributions are not normal, we used the Mann-Whitney U rank test for comparisons of the mean diameters of the following vessels between the controls and the patients with HHT: superior mesenteric artery; common hepatic artery; left and right branches; portal trunk; left and right branches and hepatic veins.
Interobserver agreement
The weighted $\kappa$ statistic was used to measure the degree of agreement between the two observers in identification of the following: nodular hyperplasia; ischemic cholangitis; hepatic telangiectases; aneurysm of the splanchnic arteries; dilatation of the common hepatic artery; anatomical variants of hepatic arteries and arterioportal or venous fistulas and their localizations.

For all statistical analyses, a $P$ value less than 0.05 was considered a statistically significant difference. All statistical analyses were performed using commercially available software (Visual Stat Version 6.0.3261, Visual Stat Computing, Inc., USA).

Results
Hepatic abnormalities were found in 91% of the HHT patients ($N = 21$). Telangiectases were found in 91.3% ($N = 21$) in the form of star-shaped lesions with low-signal intensities on $T_1$-weighted sequences and high-signal intensities on $T_2$ and random dispatching. After contrast injection, telangiectases appeared as small irregular hypervascular foci in arterial-phase sequences and as homogeneous with the parenchyma in portal-phase sequences (Fig. 1).

RHN was seen in 73.9% ($N = 17$) and was always multiple (mean number: 3.2), with diameters ranging from 1 to 6 cm (mean diameter: 2.8 cm) (Fig. 2) and iso-intense on $T_1$- and $T_2$-weighted imaging.

Ischemic cholangitis was diagnosed in 39% ($N = 9$) and was associated with irregular biliary ducts, strictures, upstream dilatation and a "pruned tree" appearance on the MR scan (Fig. 3).

Mann–Whitney U test results for vessel measurements are presented in Table 1. The diameters of the hepatic arteries and veins were statistically significantly larger in patients with HHT compared with those in the controls, according to both radiologists ($P < 0.001$). However, there was no significant difference in the diameters of the portal veins between the two study groups. Common hepatic arteries with diameters greater than 7 mm were found in 69.6% of the patients with HHT and in none of the controls.

Splanchnic aneurysms were found in eight patients (five splenic and three hepatic). These appeared as focal, fusiform or sacciform dilatations, with high-signal enhancement in arterial-phase sequences after contrast the same information, including the large, tortuous-hepatic artery with a diameter of 10 mm (arrow) and a left arterioporal fistula (curved arrow).

Patient de 45 ans, atteinte d’une télangiectasie hémorragique hériditaire avec une fistule artérioporaire, des télangiectasies et une artère hépatique dilatée. a: IRM en séquence pondérée $T_2$, coupe axiale: multiples lésions en hypersignal $T_2$ (flèche courbe) ; b: angio-IRM au temps artériel avec reconstruction en projection d’intensité maximale dans le plan coronal qui montre des lésions hypervasculaires correspondant à des zones télangiectasiques (flèche jaune). A noter une opacification précoce de la branche portale gauche en rapport avec une fistule artérioporaire (flèche rouge) et une dilatation de l’artère hépatique large (flèche blanche) ; c: angio-IRM avec reconstruction volume rendu (VR) : aspect dilaté et tortueux de l’artère hépatique (10 mm de diamètre) (flèche) et la fistule artérioporaire gauche (flèche courbe).
Figure 2 A 52-year-old man with known HHT, multiple regenerative-nodular hyperplasia and telangiectases. a: transverse T2-weighted sequences show large homogeneous lesions (arrows) with iso-intense and central hyperintense signalling on T2 and hyposignalling on T1; b: transverse nonenhanced T1-weighted sequences show large homogeneous lesions (arrows) with iso-intense and central hyperintense signalling on T2 and hyposignalling on T1; c: transverse fat-saturated T1-weighted late injection-phase sequences show enhancement of the central component and telangiectases.

Figure 3 A 50-year-old woman with known HHT, cholangitis and right arterial-to-hepatic vein fistula: coronal RARE magnetic resonance cholangiopancreatographic sequence shows a central stricture (arrow) and dilatation (curved arrow) of the biliary tract with a ‘‘pruned tree’’ appearance.

Patient de 52 ans atteint d’une télangiectasie hémorragique héréditaire avec nodules hépatiques multiples et télangiectasies. IRM en séquence pondérée T2 et T1 non injecté en coupes axiales : multiples lésions en isosignal avec hypersignal central T2 (a) et hyposignal T1 (b) (flèches). Rehaussement de la zone centrale après injection de gadolinium sur les séquences pondérée en T1 après suppression de graisse (c). Les télangiectasies sont également visibles.

administration (Fig. 4). Variant hepatic-artery anatomy was seen in 10 cases (43.4%), with 50% involving the left hepatic artery (types II and V of Michels’ classification).

Simultaneous enhancement of both hepatic veins and arteries was observed in 19 patients (82.6%). Arteriosystemic-venous shunts were seen in the three hepatic veins in 73.7% (N = 14), in the left and middle hepatic veins in 15.8% (N = 3) and in one vein in 10.5% (N = 2) (Fig. 3). Simultaneous enhancement of the portal branches and hepatic arteries was seen in 11 patients (47.8%) and was bilateral in five (45.4%), right-sided in five (45.4%) and left-sided in one (9.2%) (Fig. 4). All of these patients had an associated arteriovenous shunt. In contrast, no intrahepatic spontaneous portosystemic venous shunts were detected.

Two patients were submitted for orthotopic liver transplantation and examination of the liver explant confirmed the preoperative descriptions of the lesions based on the MRI studies.
Table 1  Vessel diameters in hereditary hemorrhagic telangiectasia and control groups and Mann–Whitney U test results.

<table>
<thead>
<tr>
<th>Reader 1</th>
<th>Controls (mm)</th>
<th>U test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 2</td>
<td>Controls (mm)</td>
<td>U test results</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vessel</th>
<th>HHT (mm)</th>
<th>Controls (mm)</th>
<th>U test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td>7.52 ± 1.04</td>
<td>6.9 ± 0.52</td>
<td>NS</td>
</tr>
<tr>
<td>CHA</td>
<td>8.69 ± 1.63</td>
<td>5.17 ± 0.44</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>RHA</td>
<td>6.63 ± 1.17</td>
<td>3.82 ± 0.44</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>LHA</td>
<td>5.08 ± 0.77</td>
<td>2.69 ± 0.33</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>PT</td>
<td>12.9 ± 1.17</td>
<td>12.5 ± 0.81</td>
<td>NS</td>
</tr>
<tr>
<td>RPB</td>
<td>8.43 ± 0.97</td>
<td>9.82 ± 0.89</td>
<td>NS</td>
</tr>
<tr>
<td>LPB</td>
<td>8.72 ± 1.37</td>
<td>8.6 ± 0.79</td>
<td>NS</td>
</tr>
<tr>
<td>RHV</td>
<td>11.13 ± 1.5</td>
<td>8.65 ± 1.18</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>MHV</td>
<td>9.08 ± 1.3</td>
<td>5.6 ± 0.88</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>LHV</td>
<td>7.47 ± 1.36</td>
<td>4.95 ± 0.95</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Interobserver agreement

This is summarized in Table 2.

Discussion

HHT, or Rendu–Osler–Weber disease, is a systemic familial-fibrovascular dysplasia characterized by telangiectases, aneurysms and arteriovenous malformations. Its clinical presentation varies greatly, depending on the number, type and location of telangiectases and on the larger visceral-vascular malformations. Curacao criteria are used for the clinical diagnosis of HHT [25]. Hepatic involvement is determined using color-Doppler ultrasound, multidetector CT or MRI. There are few reports of the value of MRI in this disease [5,17,18,26], despite the fact that the technique allows imaging of the liver parenchyma, biliary tract and hepatic vessels in appropriate sequences. MR cholan-
Hereditary hemorrhagic telangiectasia

Parenchymal abnormalities encountered in HHT are of two types: telangiectases and RNH [2]. Telangiectasia is the primary lesion of HHT, arising from dilatation of postcapillary venules that directly fuse with arterioles, bypassing the capillary system [28]. The frequency of telangiectases is estimated to be 90% in HHT patients with liver involvement [5,10,15,26] and is thought to be a consequence of a disorder of angiogenesis-control mechanisms [2]. In our study, the frequency was estimated to be 91.3% with good interobserver agreement ($\kappa = 0.62$). RNH refers to a localized proliferation of hepatocytes and their supporting stroma in response to significant liver injury [29]. Regenerative nodules are typically multiple and arise in response to venous obliteration and its consequent ischemia. In HHT, both regenerative nodules (RN) and focal-nodular hyperplasia (FNH) of the liver can occur and, to differentiate the former from the latter, RN is usually multiple with diffuse deformation of the liver surface [29]. In MRI, RN are hypo/intense on T$_1$WI and iso- or slightly hyperintense on T$_2$WI, with central hyperintense signalling on T$_2$ and hypointense signalling on T$_1$. Postcontrast images show intense-homogeneous enhancement, with enhancement of the central area persisting in delayed phase. In our study, the diagnosis of RNH was seen in 73.9% with good interobserver agreement ($\kappa = 0.63$).

Four types of vascular abnormalities are encountered in HHT: arterial dilatation and tortuosity; arterial aneurysm; variant hepatic-artery vasculature and shunts [2]. As with hepatic veins, analysis of the hepatic-artery diameter reveals a statistically significant difference between patients with HHT compared with the control population. Such an increase in diameter is thought to be a consequence of an increased flow in the hepatic artery and veins induced by intrahepatic fistulas [5,12,26]. A common hepatic-artery diameter greater than 7 mm is seen in 70% to 90% of cases [5,15,16,26]. We found this abnormality in 69.6% of our patients with HHT with good interobserver agreement ($\kappa = 0.62$). The presence of anatomical variations in hepatic-arterial vascularization was found in 43.4% ($\kappa = 1$) compared with 26% in the controls. Arterial variants also appear to be more frequent in HHT with liver involvement [5]. However, this observation could be a bias due to the increased vessel diameters seen in HHT patients, which could explain their more frequent visualization. Nevertheless, the presence of anatomical variants is important, especially before liver transplantation. Early enhancement of venous structures in the arterial phase suggests arteriovenous fistula, a sign that was never seen in the controls. Arteriosystemic-venous shunts are particularly common, identified in 50 to 64% on conventional angiography in cases of liver HHT [5,26]. After consensus, this sign was found in 82.6% of our HHT patients. This type of fistula provides a left-to-right vascular shunt, bringing the risk of a hyperdynamic circulatory state and high-output congestive-heart failure. Arterioportal shunts are less common, being identified in 30% [26], but are more frequently seen in patients with cirrhosis and/or hepatocellular carcinoma [24]. In our patients, arterioportal fistulas were suspected in 47.8%. This discrepancy with the literature could be explained by the method of analysis. We included segmental hepatic and portal veins, which allowed the appearance of peripheral enhancement. Our results are similar to those observed in a large series using multidetector CT [15]. Moderate interreader agreement was seen in the detection of fistulas. Concomitant reading of perfusion times is necessary to characterize the segmental hepatic and portal venous times before researching the possible early enhancement of these structures in the arterial phase. Nevertheless, the frequency of intrahepatic fistulas in cases of HHT is far greater than in the general population. Although symptoms may be difficult to identify, it is important to detect liver involvement in HHT as it can lead to cardiac failure [5,7,11].

Other symptoms, such as portal hypertension, encephalopathy, cholangitis and cirrhosis have also been described [5,33]. These clinical conditions are secondary to the vascular modifications seen in this disease and liver transplantation is considered the only remaining therapeutic option in patients with advanced symptoms, such as ischemic biliary necrosis, high-output cardiac failure or portal hypertension [25]. However, oesophageal varices can be treated with endoscopic or medical treatments; cardiac failure can also be medically treated [28].

The main limitations of the present study are the absence of angiographic confirmation of the MRA findings and the lack of a radiological/pathological correlation based on liver-biopsy findings. Nevertheless, two patients were submitted
for orthotopic-liver transplantation and examination of their liver explants confirmed the preoperative description of the lesions based on the imaging studies. Characteristic vascular alterations, including large intraportal dystrophic vessels, telangiectatic capillaries at the periphery of portal spaces and areas of sinusoidal dilatation were also present. In both these patients, liver nodules, presenting macroscopically and histologically similar to those of focal RNH of the liver, were identified. In one case, biliary cholangitic-type lesions were diagnosed. Another study limitation is that our controls did not include patients with other suspected liver diseases.

The main purpose of the present study was to propose an approach for screening all of the hepatic alterations encountered in HHT by MRI alone and to delineate the hepatic MR findings. Such findings in the absence of other causes of liver disease, if corroborated by clinical findings, strongly suggest hepatic involvement. Because of the potential for cardiac or hepatic failure, determining the presence of liver involvement in patients with HHT is crucial. Even if no clinical symptoms of liver disease are present, imaging methods should be used to ascertain liver involvement. Although multidetector CT has recently demonstrated its usefulness in HHT explorations, MRI should be considered an alternative one-step method for examination of the liver without the use of nephrotoxic contrast agents and ionizing radiation.

References


