Differentiation Between Focal Nodular Hyperplasia and Hepatic Adenoma using Gadobenate Dimeglutamine-enhanced MR Imaging.

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Focal nodular hyperplasia (FNH) is a benign tumor-like hepatic lesion composed by hepatocytes, bile ducts, blood vessels and Kupffer's cells. Frequently presents a fibrous central scar forming fibrous septum, dividing the lesion into small nodules composed by proliferated hepatocytes that lack normal hepatic architecture. It's been suggested that FNH results from a congenital vascular malformation that induce a focal hepatocellular hyperplasia. All these alterations lead to a slow biliary excretion. Since FNH is not associated with any malignancy and has only a minimal tendency for necrosis and hemorrhage, confirmed FNH is almost always managed conservatively; surgical resection is rarely indicated. The hepatic adenoma (HA) is an uncommon primary benign hepatocellular lesion composed by layers of normal hepatocytes that lack the normal acinar architecture of the surrounding hepatic parenchyma. Although hepatic adenoma is uncommon, its differentiation from FNH is clinically important because (a) it may undergo malignant degeneration into hepatocellular carcinoma and (b) it is much more likely to bleed than FHN, potentially resulting in life-threatening hemoperitoneum. Rapid increase in the size of HA stimulated by increased hormonal levels during pregnancy or by its strong association with exogenous therapy with estrogen or an anabolic steroid is well described in the literature and is associated with increased risk of rupture. For these reasons, a solitary HA is often resected. Frequently, the diagnosis of FNH or HA can be aided by the presence of characteristic lesion features such as a central scar in the case of FNH or a heterogeneous appearance due to intralesional hemorrhage in the case of HA. However, it may be difficult to recognize a HA because its features at dynamic MR imaging performed with extracellular gadolinium chelates overlap substantially with those of FNH (Table 1). This problem is particularly difficult in small atypical lesions that do not have a central scar (in the case of FNH) or are non hemorrhagic (in the case of HA). Gadobenate dimeglumine is a hepatobiliary-specific agent, taked up to varying degrees by functioning hepatocytes and excreted in the bile. This agent is based on gadolinium and has seven unpaired electrons which give the agent their paramagnetic properties. Admininstered intravenously, is initially distributed in the extracellular fluid compartment, just as classic extracellular fluid agents do, and is subsequently taken up by hepatocytes, providing the dual benefit of dynamic imaging capability as well as delayed hepatobiliary phase imaging. FNH lesions are composed of functioning hepatocytes and bile ducts and are, therefore, typically isointense or hyperintense relative to normal liver parenchyma in the hepatocellular phase. At hepatocellular phase imaging, HA typically appear hypointense relative to normal liver. One explanation of this phenomenon holds that HA contain functioning hepatocytes but not bile ductules, and hepatic-specific contrast agents cannot be excreted. This are the reasons why Gadobenate dimeglumine is been used widely to differentiate NFH from HA lesions. The next study presents the experience of our center using gadobenate dimeglumine imaging for characterization and differentiation between FNH and HA.
Table 1

Signal Intensity Patterns in Common Liver Lesions with Standard MR Imaging and Hepatocellular Phase Imaging with Hepatocyte-specific contrast agents (HSCAs)

<table>
<thead>
<tr>
<th>Hepatic Lesion</th>
<th>Standard MR Imaging</th>
<th>HCP with HSCAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unenhanced T1</td>
<td>Unenhanced T1</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Adenoma</td>
<td>↑ or →</td>
<td>↑ or →</td>
</tr>
</tbody>
</table>

Note: The table includes only the most common signal intensity patterns. Directional arrows indicate isointensity (→), hypointensity (↓), and hyperintensity (↑) relative to the intensity of normal liver parenchyma.

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Methods and Materials

Study Population

This study includes all the patients who were booked in our radiology service for a liver MRI, to discriminate between FNH and HA, in which the used contrast agent was Gadobenate dimeglumine, from November 2009 to August 2012. A total of 12 patients were included (11 women, one man; mean age, 38 years ± 7.09 [± standard deviation]; range, 25-47 years). The proportion of women to men was significantly different, which reflects the greatest prevalence of these lesions among the female population. Patients were included as part of routine clinical practice, in most cases, to characterize a hepatic lesion previously seen with other imaging techniques (US, CT or MR) as a part of the initial study of a hepatic lesion or as a follow-up study of an already known lesion. Of the 12 patients, 3 had pain in the upper abdomen when they first consult. The remaining 9 patients were asymptomatic, and the study was initiated for hepatic blood test alterations or after incidental findings at abdominal imaging performed for other reasons. All the female patients had a history of taking oral contraceptives. One of the patients had a history of thyroid cancer, and other, endometriosis.

Confirmation of the lesions was performed after surgical resection (two FNHs in two patients, and one HA in one patient) and percutaneous biopsy (one patient). The remaining patients were classified according to the imaging findings and controlled with successive MR studies.

MR Imaging Protocol

The same MR imaging protocol was used in each examination. All patients were imaged with a superconducting imager (Phillips Healthcare) operating at 3T by using a body-array coil. MR imaging was performed by using T2-weighted turbo spin echo sequences with and without fat saturation (repetition time msec/echo time msec, 653/80; flip angle, 125°) and T1-weighted gradient-echo (GRE) in-phase (89/4.6; 80° flip angle) and out-of-phase (89/2.3, 80° flip angle). Images were acquired prior to the administration of contrast agent; during the dynamic phase of contrast enhancement (T1-weighted GRE images) at 25 seconds (arterial phase), 60 seconds (portal venous phase), and 4 minutes (equilibrium phase) following intravenous bolus (3-4 mL/sec) administration of gadobenate dimeglumine (Multihance®) at a dose of 0.2 mmol per kilogram of body weight; and during a later delayed hepatobiliary phase (T1-weighted GRE images only) at one or more time points between 40 min to 1 hour. Post contrast images were acquired with fat suppression. The section thickness was 6 mm. A matrix size of 224/147 was used with a rectangular field of view of 350-400 mm.
Image Analysis

Images were evaluated in consensus by four radiologists in terms of the intensity of the lesion signal on in-phase MR images acquired before gadobenate dimeglumine administration and during the dynamic and delayed phases of the MR study. Images were also evaluated for the presence of a central scar. In each case, assessment of images from each patient was performed in a similar manner to that which occurs in routine practice, with all the images sets available for simultaneous evaluation. After this, the enhancement findings were matched with the final diagnosis.

Statistical Analysis

The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for the differentiation of FNH from HA lesions were determined on the basis of post contrast enhancement patterns on the delayed MR images. A true-positive lesion was a lesion with a final diagnosis of FNH and was isointense or hyperintense to the surrounding liver parenchyma, a true negative lesion was a lesion with a final diagnosis of HA and was hypointense to the surrounding liver parenchyma, a false-positive lesion was a lesion with a final diagnosis of HA and was isointense or hyperintense to the surrounding liver parenchyma, and a false-negative lesion was a lesion with a final diagnosis of FNH and was hypointense to the surrounding liver parenchyma.
Results

Pre contrast Unenhanced Imaging
On pre contrast T2-weighted fast spin echo, all FNH lesions were either slightly hyperintense or isointense to the surrounding parenchyma. On the corresponding pre contrast T1-weighted GRE images, all the lesions were isointense or slightly hypointense. A hyperintense central scar was apparent on pre contrast T2-weighted images in 5 FNH lesions. Hypointense central scars on pre contrast T1-weighted GRE images were detected in 4 lesions. Concerning HA, all lesions were either slightly hyperintense or isointense to the surrounding parenchyma on pre contrast T2-weighted images. On pre contrast T1-weighted GRE images, 3 lesions appeared slightly hypointense, and one lesion appeared hyperintense.

Post contrast Dynamic Phase Imaging
During the arterial phase, all of the FNH lesions showed marked homogeneous hyperintensity to the surrounding normal liver parenchyma (Fig 1c,2c,5c). Slight hyperintensity that persisted into the portal venous and equilibrium phase was noted for 7 and 5 lesions respectively. Two lesions were isointense on both, portal and equilibrium phases, and two just in equilibrium phase. A hypointense central scar was noted in 5 of 9 lesions on arterial phase images. All of this scars was seen hyperintense in equilibrium phase. The enhancement behavior of HA was very similar to that of FNH on dynamic phase images. Overall, 3 of 4 lesions were markedly hyperintense to the normal parenchyma on arterial phase images while the remaining small HA lesion appeared isointense. On portal and equilibrium phases, the four cases have a different behavior: one hypointense in both phases; one isointense in both phases; one hyperintense in the two phases and one with hyperintensity in portal venous phase, and isointense in equilibrium phase.

Post contrast Hepatobiliary Phase Imaging
On delayed phase T1-weighted GRE images acquired 45 min to 1 hour after administration of gadobenate dimeglumine, 8 of 9 FNH lesions appeared either hyperintense or isointense to the surrounding enhanced normal parenchyma. An atypical heterogeneous image appeared (Fig. 5), showing hypointense and hyperintense areas in the same lesion. A hypointense central scar was noted in 5 of 9 lesions overall on delayed phase images. All HA lesions were hypointense to the enhanced normal liver parenchyma on post contrast delayed images.

Accuracy
By taking lesion hyperdensity or isodensity on delayed images after gadobenate dimeglumine administration as indicative of FNH (a true-positive lesion) and lesion hypointensity as indicative of HA (a true-negative lesion), the sensitivity, positive predictive value, negative predictive value and overall accuracy for the differentiation of FNH from HA were 88%, 100%, 100%, 75% and 91%, respectively.
**Fig. 1:** MR images in a 40-year-old woman with typical FHN, asymptomatic, and a 20 year history of oral contraceptive use. (a) Transverse T1-weighted image shows two very faintly hypointense lesions. One (arrow) of approximately 50 cm in liver segment IV and adjacent to this one, other of 20 cm in liver segment VIII. (b) On transverse T2-weighted image, the lesions are faintly hyperintense to the surrounding parenchyma. (c) On corresponding post contrast arterial phase T1-weighted image, the lesions demonstrate strong homogeneous enhancement, and it shows another lesion of 30 cm in liver segment V. The three of them retains a faint hyperintensity during subsequent (d) portal venous and (e) equilibrium phases. A characteristic central scar (arrow) in d) is clearly seen as hypointense in arterial phase and slightly hyperintense in equilibrium phase. (f) Although FHN diagnosis is likely based on dynamic phase images alone, confirmation comes from a marked hyperintense appearance of the lesion on hepatobiliary phase fat-suppressed T1-weighted image acquired 45 minutes after gadobenate dimeglumine injection. The central scar appears faintly hypointense in delayed hepatobiliary phase.

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Fig. 2: MR images in 39-year-old asymptomatic man. (a) No lesion is evident on unenhanced transverse T1-weighted image. (b) On unenhanced transverse T2 image, a very faintly hypointense lesion of approximately 8cm is evident in liver segment IVa. (c) On corresponding post contrast arterial phase T1 weighted image, the lesion demonstrates strong enhancement. The lesion appears only slightly hyperintense to the surrounding normal liver parenchyma during (d) portal venous and (e) equilibrium phase. Accurate differentiation of HA from FNH is not possible on the basis of only unenhanced and post contrast dynamic phase images. (e) On corresponding T1-weighted image acquired 45 min. After injection of gadobenate dimeglumine, the lesion is homogeneously isointense to the normal parenchyma. The characteristic central scar very slightly insinuates on T2, arterial, venous, equilibrium and hepatobiliary phases (arrows).

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Fig. 3: MR images in a 28-year-old woman with LA, an 8-year history of oral contraceptive use, and pain in the upper abdomen. (a) Transverse T1-weighted image clearly reveals a 15cm hypointense lesion, originated on the caudate lobe. (b) On unenhanced transverse T2-weighted image, this lesion is isointense to the normal liver parenchyma. (c) On corresponding post contrast arterial phase, T1-weighted image, the lesion demonstrates strong enhancement, appearing slightly hypointense to the surrounding normal liver parenchyma during (d) portal and (e) equilibrium phases. (f) On corresponding T1-weighted image acquired 1 hour, after injection of gadobenate dimeglumine, the lesion is homogeneously hypointense to the normal parenchyma, which enables the differential diagnosis of FNH to be excluded.

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Fig. 4: MR images in a 47-year-old woman with HA, without history of oral contraceptive use, and mild pain in the upper abdomen. (a) Unenhanced transverse T1-weighted GRE image reveals one hypointense lesion (arrow). (b) On transverse T2-weighted image, the lesion is hyperintense. (c) Only minimal enhancement of this lesion is seen on corresponding T1 weighted post contrast arterial phase GRE image. This lesion is already faintly hypointense to the normal liver parenchyma during (d) portal venous phase and (e) equilibrium phase. (f) During hepatobiliary phase at 50 min after gadobenate dimeglumine administration, this lesion is very clearly hypointense to the surrounding enhanced normal live parenchyma.

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Fig. 5: MR images in a 35-year-old asymptomatic woman with atypical FHN. (a) Unenhanced transverse T1-weighted GRE image reveals a hypointense lesion of approximately 43 mm in liver segment V. (b) On transverse T2-weighted image the lesion is faintly hyperintense to the surrounding parenchyma. (c) On corresponding post contrast arterial phase T1-weighted GRE image, the lesion shows strong homogeneous enhancement and appears faintly hyperintense in during subsequent (d) portal venous phase and (e) equilibrium phase. No central scar is apparent and accurate diagnosis is difficult on the basis of unenhanced and dynamic phase images alone. (e) On corresponding T1-weighted GRE image acquired 45 min after injection of gadobenate dimeglumine, the lesion has an atypical appearance with nodular areas of isoointensity and slight hyperintensity interspersed with other hypointense areas, which results in the lesion to appear predominantly hypointense relative to the surrounding normal parenchyma. Findings was interpreted as HA and surgical resection was performed.

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Conclusion

Today it's well known the importance of differentiate FNH from HA, because of the potential of malignancy and complications linked to this last lesion, although they both are considered benign. The clinical need is, therefore, find the way to accurately differentiate one from the other at noninvasive diagnostic imaging before need a more invasive procedure, like biopsy or surgery. Unfortunately, the available techniques today doesn't allowed a specific differential diagnosis in this cases, especially with atypical lesions. Both lesions enhanced strongly during the arterial phase and then either retain a hyperintense appearance or demonstrate isointensity with the normal liver parenchyma during subsequent portal venous and equilibrium phases.

The findings in this study demonstrate that a highly accuracy for the differentiation between FNH and HA can be made obtaining images on a delayed hepatobiliary phase, 45 minutes to 1 hour after the intravenous administration of gadobenate dimeglumine, with overall accuracy of 91%. It is just to mention that, been a small study with a reduced amount of patients, this accuracy was highly influenced by the misinterpretation of the results in one case.

Diagnose mistakes are important to review, because of the information they can provide us. One patient in this serie was diagnosed of HA, by the findings on delayed hepatobiliary phase of a gadobenate dimeglumine enhanced MR (Fig 5.), and ended up been operated. The posterior pathological analysis of the surgical piece informed a FNH. Analyzing the images, the findings in the delayed phase were not the typical homogeneous enhancement, but a heterogeneous atypical enhancement. That's why we think that while lesions with a single minor atypical feature in the hepatocellular phase should be monitored with MR imaging, lesions with an atypical feature such as uniform hypointensity or heterogeneous enhancement in the hepatocellular phase should not be quickly diagnosed as FNH or HA; instead, additional imaging work-up with modalities such as contrast-enhanced ultrasonography should be considered.

Although the results clearly demonstrate that FNH and HA lesions could be distinguished readily on delayed phase images after gadobenate dimeglumine administration, this study as many others in this area, is limited by the absence of histological verification of FNH lesions. However, a systematic follow up of these patients, after the analysis of the findings in this kind of MR study, its been a successful strategy in our experience. Most of the studies performed in this area use long protocols (3 hours the majority of them) to capture images from the hepatobiliary phase, producing a logistical problem because of the increased waiting time for each patient. In our study, we found that a shorter protocol (45 min to 1 hour) provide good quality images that reflect quite well the characteristics of the studied lesions, with the advantage of improving the logistical management of the patients, and because of that, the efficiency of the system.

In conclusion, our experience in the use of gadobenate dimeglumine (Multihance®) is been considerably helpful to differentiate between FNH from HA, and our protocol with a
shorter waiting time (45 min to 1 hour) to obtain the hepatobiliary phase images, is been as effective as longer protocols exposed in other series.
References


