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MR Characterization of Focal Nodular Hyperplasia: Gadoxetic Acid versus Superparamagnetic Iron Oxide Imaging

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Purpose: We evaluated the diagnostic efficacy of gadoxetic acid- and superparamagnetic iron oxide (SPIO)-enhanced magnetic resonance (MR) imaging for focal nodular hyperplasia (FNH).

Materials and Methods: We retrospectively evaluated 11 patients with 11 FNHs. Both gadoxetic acid- and SPIO-enhanced MR imaging were performed. A 3-dimensional (3D) volumetric interpolated breath-hold examination was used with the gadoxetic acid dynamic study. SPIO-enhanced MR imaging included T2- and T2*-weighted images. We quantitatively and qualitatively compared lesion-specific enhancement of both contrast media.

Results: The mean signal-to-noise (S/N) ratio of the FNH lesions differed significantly on pre- and postenhanced imaging of each contrast medium (P < 0.05); mean contrast-to-noise (C/N) ratio did not (P > 0.05). All observers described all lesions as hyperintense in the arterial phase on gadoxetic acid-enhanced MR imaging and observed the presence of central scar, fibrous septa, and rim most clearly in gadoxetic acid-enhanced hepatobiliary phase images.

Conclusion: Gadoxetic acid-enhanced MR imaging was more useful than SPIO-enhanced MR imaging in characterizing FNH.

Keywords: focal nodular hyperplasia, gadolinium ethoxybenzyl diethylenetriamine pentaaacetic acid, gadoxetic acid, magnetic resonance imaging, superparamagnetic iron oxide

Introduction

Focal nodular hyperplasia (FNH) was first reported by Edmondson in 1956,1 is frequently detected following hemangioma,2 represents a local hyperplastic response of hepatocytes to congenital vascular abnormalities,3 and is observed in middle-aged women.4 Fifty percent of FNH demonstrate a central scar.4 The vascular nature of FNH makes its differentiation from hepatocellular carcinoma important. Recent advances in diagnostic imaging modalities have increased the frequency with which this entity is encountered.

Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (gadoxetic acid, EOB Primovist®, Bayer Schering Pharma, Osaka, Japan) is a liver-specific contrast medium that enables dynamic study with bolus injection, similarly to nonspecific extracellular contrast medium.5,6 The hepatobiliary phase begins 1.5 min after injection of contrast medium and continues for 2 hours; peak liver signal intensity is obtained 20 min after injection.6 Contrast medium accumulates in the liver parenchyma and appears hypointense compared with the surrounding liver parenchyma 20 min after injection.7 FNH shows a high prevalence of iso- or hyperintensity in the hepatobiliary phase.8

Superparamagnetic iron oxide (SPIO) particles have also been used to diagnose FNH. SPIO particles are taken up by Kupffer cells and produce low signal intensity on T2-weighted images, owing to shortening of the T2 relaxation time. FNH contains more Kupffer cells than malignant hepatocellular lesions, such as hepatocellular carcinoma,9 so SPIO particles permit differentiation of benign and malignant lesions.

Because no reports compare the diagnostic effica-
cy of gadoxetic acid- and SPIO-enhanced magnetic resonance (MR) imaging in FNH, we set out to evaluate which medium is most suitable for diagnosing FNH.

Materials and Methods

Subjects

Our institutional review board approved this retrospective study, and informed consent was waived. From our institutional radiological records of January 2006 and June 2010, we selected for study 11 patients (8 men, 3 women; aged 33 to 77 years, mean, 49 years) with 11 FNH lesions who had undergone both gadoxetic acid- and SPIO-enhanced MR imaging, contrast-enhanced ultrasound with or without dynamic computed tomography (CT), or extracellular gadolinium chelate dynamic MR imaging and who had been observed more than one year.

Three of the 11 lesions were pathologically confirmed by biopsy. The other eight were diagnosed based on imaging findings of spoke wheel appearance and strong enhancement in arterial phase and iso-echo in Kupffer phase by contrast-enhanced ultrasound and/or clear enhancement in the arterial phase and isodensity compared with the surrounding liver parenchyma in the equilibrium phase on dynamic CT or MR imaging using extracellular nonspecific contrast medium.

We were able to confirm no changes in the lesions after one year of observation. The maximum dimensions of lesions, as measured by ultrasonography, were 8 to 36 mm (mean ± standard deviation; 22 ± 11 mm).

Magnetic resonance imaging

MR images were obtained using a 1.5-tesla superconductive MR imaging system (Avanto; Siemens, Erlangen, Germany). T1-weighted images (T1WI) included in- and opposed-phase images. The T1WI parameters (in- and opposed-phase) were: repetition time/echo time (TR/TE), 120 ms/4.76, 2.38 ms; flip angle, 75°; one averaging; matrix, 256 × 140; parallel acquisition technique (PAT) factor 2 with generalized autocalibrating partially parallel acquisition (GRAPPA) algorithm; slice thickness, 6 mm; slice gap, 1.2 mm; and acquisition time, 13 s. The T2WI parameters were: TR/TE, 150 ms/1.78 ms; flip angle, 15°; matrix, 256 × 85 (%); PAT factor, 2; slice thickness, 3 mm; and acquisition time, 20 s. The monitoring scan technique (CARE Bolus method, Siemens) was used to obtain the optimal arterial phase. The hepatobiliary phase was obtained by 3D-VIBE 20 min after injection of the contrast material.

Bolus-injectable ferucarbotran (Resovist®, Bayer Schering Pharma, Osaka, Japan) was used for SPIO-enhanced MR imaging. Each patient received a total dose of 1.4 mL of ferucarbotran manually administered or rapidly administered at a rate of 2 mL/s using power injector followed by 20 to 40 mL of physiological saline. Three minutes after administration, T1-weighted images were obtained. The SPIO-enhanced T1WI parameters were: TR/TE, 130 ms/2.0 ms; flip angle, 90°; one averaging; matrix, 154 × 256; PAT factor 2 with GRAPPA algorithm; slice thickness, 6 mm; slice gap, 1.2 mm; and acquisition time, 24 s. Ten minutes after administration, T2-weighted fast spin echo images and T2*-weighted images were taken. The T2*-weighted image parameters were: TR/TE, 150 ms/9 ms; flip angle, 30 or 60°; matrix, 138 × 256; slice thickness, 6 mm; one averaging; 7 slices; bandwidth, 60 Hz per pixel; and acquisition time, 21 s. Acquisition of T2*-weighted images of the entire liver required 3 scans.

The mean interval between gadoxetic acid-enhanced MR imaging and SPIO-enhanced MR imaging was 9 months (one to 42 months).

Image analysis

We quantitatively compared lesion-specific enhancement by both liver-specific contrast media using signal-to-noise (S/N ratio) and contrast-to-noise (C/N ratio) ratios, which we calculated as: S/N = signal intensity of tumor/noise, and C/N = (signal intensity of tumor—signal intensity of liver parenchyma)/noise.

We used a standard deviation of the signal intensity of the liver parenchyma as an estimate of local noise because we employed parallel imaging. A radiologist with 20 years’ experience in diagnostic imaging of the liver set a circular region of interest (ROI) to contain as much of the lesion as possible to measure lesion signal intensity on 3D-VIBE im-
Fig. 1. (a) Signal-to-noise (S/N) and (b) contrast-to-noise (C/N) ratios of lesion on pre- and post-gadoxetic acid-enhanced T1-weighted images. Between the pre- and post-gadoxetic acid-enhanced T1-weighted images, the mean S/N ratios were 22.0 ± 7.1 and 42.9 ± 22.9. There was a marked difference in S/N ratios between pre- and post-gadoxetic acid-enhanced T1-weighted images (P < 0.05). The mean C/N ratios on pre- and post-gadoxetic acid-enhanced T1-weighted images were statistically significant (P < 0.05).
Fig. 2. (a) Signal-to-noise (S/N) and (b) contrast-to-noise (C/N) ratios of lesion on pre-and post-gadoxetic acid-enhanced T1-weighted images. Between the pre- and post-gadoxetic acid-enhanced T1-weighted images, ratios of S/N differed significantly ($P < 0.05$); ratios of C/N did not ($P > 0.05$).

- $5.3 \pm 4.2$ and $-4.9 \pm 11.4$. The C/N ratios did not differ significantly between the pre- and post-gadoxetic acid-enhanced T1-weighted images ($P > 0.05$) (Fig. 2).

The mean C/N ratio of the post-SPIO-enhanced $T_2^*$-weighted image was $6.6 \pm 9.9$. C/N ratios did not differ significantly among the post-SPIO-enhanced $T_2$-weighted, post-SPIO-enhanced $T_2^*$-weighted, and gadoxetic acid-enhanced images ($P > 0.05$) (Fig. 3).

Qualitative analysis

All observers classified most lesions as iso- or hyperintense on the pre- and post-SPIO-enhanced $T_2$-weighted images. Moreover, all observers described all lesions as iso- or hypointense on pre-gadoxetic acid-enhanced T1-weighted images and hyperintense in the arterial phase on gadoxetic acid-enhanced MR imaging. Lesion intensity varied in SPIO-enhanced $T_2^*$-weighted images and gadoxetic acid-enhanced hepatobiliary phase images (Table 1). For all 3 observers, qualitative signal intensity of lesions did not differ significantly between pre- and post-SPIO-enhanced $T_2$-weighted images ($P > 0.05$), but did differ significantly between pre- and post-gadoxetic acid-enhanced MR images ($P < 0.05$). There was no significant relationship between uptake of the 2 contrast media for any of the 3 observers.

All observers identified the presence of central scar, fibrous septa, and rim most clearly on the gadoxetic acid-enhanced hepatobiliary phase image followed by the SPIO-enhanced $T_2^*$-weighted image (Table 2, Fig. 4).

Discussion

Most cases of FNH have Kupffer cells, and about half have more Kupffer cells than the surrounding liver parenchyma. Because SPIO is taken up by Kupffer cells, SPIO-enhanced MR imaging seems an effective means of diagnosing FNH lesions. However, the dependency of lesion signal intensity on the (variable) number of Kupffer cells in the lesion makes diagnosis difficult. In the present study, lesion signal intensity varied. The evaluation of lesion vascularity is reportedly useful in diagnosing FNH using perfusion study under SPIO bolus in-
Table 1. Signal intensity of focal nodular hyperplasia (FNH) on superparamagnetic iron oxide (SPIO)- and gadoxetic acid-enhanced magnetic resonance (MR) imaging

|            | Intensity | Observer 1 | Observer 2 | Observer 3 |
|------------|-----------|------------|------------|------------|
| \(T_2\) pre | Hyper-    | 5          | 6          | 7          |
|            | Iso-      | 6          | 5          | 3          |
|            | Hypo-     | 0          | 0          | 1          |
| \(T_2\) post | Hyper-    | 4          | 4          | 6          |
|            | Iso-      | 6          | 7          | 4          |
|            | Hypo-     | 1          | 0          | 1          |
| \(T_2^*\) post | Hyper-    | 6          | 7          | 6          |
|            | Iso-      | 1          | 2          | 3          |
|            | Hypo-     | 4          | 2          | 2          |
| EOB pre-   | Hyper-    | 0          | 0          | 0          |
|            | Iso-      | 3          | 2          | 2          |
|            | Hypo-     | 8          | 9          | 9          |
| EOB arterial | Hyper-    | 11         | 11         | 11         |
|            | Iso-      | 0          | 0          | 0          |
|            | Hypo-     | 0          | 0          | 0          |
| EOB HBP    | Hyper-    | 5          | 4          | 5          |
|            | Iso-      | 6          | 5          | 3          |
|            | Hypo-     | 0          | 2          | 3          |

EOB, gadoxetic acid; HBP, hepatobiliary phase; post, post-enhancement; pre, pre-enhancement.

Table 2. Detection of central scar, fibrous septa, and rim in or surrounding focal nodular hyperplasia (FNH) by each observer on superparamagnetic iron oxide (SPIO)- and gadoxetic acid-enhanced magnetic resonance (MR) imaging

| Scar | Fibrous septa | Rim |
|------|---------------|-----|
| \(T_2\) | \(T_2^*\) | EOB | \(T_2\) | \(T_2^*\) | EOB | \(T_2\) | \(T_2^*\) | EOB |
| Observer 1 | 3 | 5 | 9 | 2 | 4 | 8 | 4 | 4 | 7 |
| Observer 2 | 3 | 8 | 10 | 2 | 5 | 7 | 2 | 4 | 7 |
| Observer 3 | 3 | 1 | 7 | 9 | 2 | 6 | 7 | 3 | 6 | 7 |

EOB, gadoxetic acid; T2, SPIO-T2; T2*, SPIO-T2*

Gadoxetic Acid-enhanced MRI of Focal Nodular Hyperplasia

Signal intensity of focal nodular hyperplasia (FNH) on superparamagnetic iron oxide (SPIO)- and gadoxetic acid-enhanced magnetic resonance (MR) imaging has shown the majority of FNH to be hypervascular in the arterial phase and iso- or hyperintense in the delayed phase.\(^{18}\) Abnormal biliary drainage is one pathological feature of FNH\(^2\) and is demonstrated by accumulation in the lesion of contrast medium that has been excreted into the bile. Gadoxetic acid resembles Gd-BOPTA as a hepatocellular-specific contrast medium and similarly enables measurement in the arterial and hepatocellular-specific (hepatobiliary) phases. The higher excretion rate of gadoxetic acid than Gd-BOPTA into the bile may cause the occurrence rate of FNH to appear higher than in the delayed phase on Gd-BOPTA-enhanced MR imaging. Most FNH lesion intensity has been classified as hyperintense, isointense, or mixed in the hepatobiliary phase, indicating the accumulation of contrast medium in hepatocytes.\(^8\) We obtained similar results in the current study. Generally, liver tumors appear hypointense in the hepatobiliary phase. However, selective hepatocyte enhancement, namely, iso- or hyperintensity in the hepatobiliary phase, appears in some liver tumors, such as in parts of hepatocellular carcinoma\(^19,20\) and hepatocellular adenoma.\(^5\)

In the present study, we more frequently observed central scar, fibrous septa, and rim on gadoxetic acid-enhanced than SPIO-enhanced MR imaging. Zech and associates also reported higher detection of the central scar in the hepatobiliary phase on gadoxetic acid-enhanced MR imaging.\(^8\) Furthermore, FNH showed hypervascularity in the arterial phase on gadoxetic acid-enhanced MR imaging. Therefore, gadoxetic acid-enhanced MR imaging is superior to SPIO-enhanced MR imaging in characterizing FNH.

Spatial resolution represents one difference in signal intensity of the lesion and its characteristic structures. Kim and associates reported the superiority of the 3D-VIBE sequence to 2D SPIO-enhanced MR imaging in terms of spatial resolution to detect hepatocellular carcinoma.\(^21\) Similarly, gadoxetic acid-enhanced MR imaging obtained by 3D-VIBE sequencing is superior to SPIO-enhanced 2D sequences in detecting FNH and detailing the internal structure of the lesion.

Our study has several limitations. Although our number of subjects was small, we believe the absence of a report of an intra-individual comparison of SPIO- and gadoxetic acid-enhanced MR imaging in diagnosing FNH underscores the importance of the present study. The number of pathologically confirmed lesions was also small because most lesions showed typical radiological findings and did not require biopsy.\(^11\) Finally, we did not adopt the optimal sequence for SPIO-enhanced MR imaging.

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Fig. 4. A 38-year-old man. (a) Pre-enhanced 3-dimensional (3D) volume interpolated breath-hold examination (VIBE) image, (b) arterial phase and (c) hepatobiliary phase on gadoxetic acid-enhanced image, (d) pre-enhanced T2-weighted image, (e) superparamagnetic iron oxide (SPIO)-enhanced T2-weighted image. A hypervascular lesion shows segment III in the arterial phase (b) on gadoxetic acid-enhanced MR imaging. Central scar, fibrous septa, and rim are clearly depicted in the hepatobiliary phase (c). The central scar is barely observed on a SPIO-enhanced T2-weighted image (e).

In the pre- and post-enhancement stages; the spin echo sequence is the optimal sequence for evaluating SPIO uptake in FNH, and T2*-weighted imaging is the optimal sequence for evaluating the structure of an internal lesion in FNH. We used a fast spin echo sequence under breath-holding to prevent motion artifact and enable a shorter examination time. Although this had the potential to weaken the susceptibility effect, we consider that there was no negative effect on the quantitative evaluation because the same sequence was performed pre- and post-enhancement. Pre-contrast T2*-weighted images were not obtained in the present study because of their poor contrast between liver and lesion.

In conclusion, gadoxetic acid-enhanced MR imaging appears more useful than SPIO-enhanced MR imaging in characterizing FNH lesions.

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