Gd-BOPTA-enhanced MR imaging in the differential diagnosis of FNH on the basis of both radiological and clinical findings

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Authors: E. Szurowska, J. M. Pienkowska, T. Nowicki, E. Izycka-Swieszewska, K. Markiet, D. Zadrozny, M. Studniarek; Gdansk/PL
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Focal nodular hyperplasia (FNH), next most frequent benign liver tumor after hemangioma, is composed of hyperplastic nodules of hepatocytes separated by fibrous septa with common central scar. Thick-walled abnormally large arteries perfusing the lesion are present in these septa. The mostly accepted pathogenesis of FNH is the reactive proliferation of the hepatocytes due to preexistent vascular malformation.

It mostly develops in women between the ages of 20 and 50. It has been reported in 0.3%-6% of general population.

Clinical symptoms and biochemical parameters in case of FNH are unspecific and diagnosis on the basis of ultrasonography and needle biopsy may cause difficulties.

The different clinical behavior and pathological features highlight the importance of differentiating FNH between other hypervascular liver lesions such as hepatic adenoma (HA), hepatocellular carcinoma (HCC), and hypervascular metastases which is critical to ensure proper treatment.

Our study was conducted on a large number of hepatic focal changes with interdisciplinary approach to the problem on the basis of both radiological and clinical picture.
Methods and Materials

In 158 consecutive patients with ambiguous focal changes in the liver observed on ultrasonography, underwent MRI of the liver with the use of hepatotropic contrast medium Gd-BOPTA (Gadobenate dimeglumine - Multihance).

The examination of the liver was performed using 1.5 T device with the use of surface or body-type coil. Non-contrast examination comprised SE sequences (TR/TE ms - 303/12, scan time - 17 sec) and Express (18000/ 80, scan time - 17 sec) in T1 and T2-dependent images in the horizontal and frontal plane as well as sequences with fat tissue saturation - FSE BH + FatSat (6500/116.8, scan time - 22 sec.). Section thickness was 4.5 - 5 mm, intersection gap - 1 mm, FOV 35 x 32 cm, matrix - 256 x 256 and 128 x 256. Contrast medium Gd-BOPTA was administered in a so-called manual bolus through venous catheter in the dose of 0.1 mmol/kg of body weight at a rate of 2 ml/s. Injection was finished with administration of 30 ml of normal saline. Arterial, venous portal and equilibrium phases were obtained after 25, 60 and 180 s from the beginning of contrast medium injection respectively. Moreover, T1-weighted sequences were repeated after 60 minutes from contrast medium injection what enabled obtaining a hepatocytic phase. The phase-encoding direction was anterior-posterior for all sequences. All images were acquired during breath-hold.

The study was prospective, MRI images were evaluated by three independent observers. Size of the found foci, their localization in the liver segments, signal intensity in T1- and T2-weighted images, type of contrast enhancement in the given phases of MRI (in the arterial, venous portal and equilibrium phases) and the presence of central scar and pseudocapsule were evaluated. Signal intensity was assessed in comparison with the liver in T1- and T2-weighted images (hypointensive, isointensive, hyperintensive, strongly hyperintensive - of a signal higher or comparable to the fat tissue). In the arterial phase, it was analyzed if a lesion enhances peripherally (ring enhancement or peripheral globular enhancement) or centrally (homogeneous enhancement or heterogeneous enhancement). In the hepatocytic and equilibrium phases, enhancement intensity of the lesion in comparison with the liver (weaker, stronger, same as in the liver) was assessed. In the venous phase, enhancement type was evaluated distinguishing the following subtypes: as in the liver, ring enhancement, enhancement progressing from the periphery, homogenous and heterogenous enhancement. In all the phases and sequences, presence of a central scar and pseudocapsule was assessed.

Altogether, 389 focal hepatic lesions were evaluated. In 89 patients, final diagnosis was based upon the histopathological examination which distinguished 21 patients with FNH, 39 subjects with HCC, 4 with adenoma and 25 with metastatic foci.
In the 69 remaining patients, the final diagnosis was based upon the clinical and imaging follow-up, among them in 30 patients with hepatic hemangiomas, 18 with FNH and 21 patients with liver metastases.

The patients were divided into two groups.

The first group was formed by 119 patients with 345 focal liver lesions of different nature than FNH (non-FNH) - 119 patients with 345 focal lesions.

The second group consisted of 39 people with 44 FNH's foci.

In non-FNH group, liver cirrhosis was recognized on the basis of biopsy in 37 subjects.

Among the patients from FNH group, slight elevation in GGTP activity was stated in 10 cases, liver cirrhosis in one person and in the remaining ones, liver profile was within the range of normal values.

Neoplastic disease in the anamnesis was reported by 6 patients in whom oncologic follow-up was the reason to perform ultrasonography of the abdominal cavity. In 17 subjects with FNH, a lesion was detected accidentally.

To find typical radiological features enabling diagnosis of FNH on the basis of MRI, statistically more common radiological features were pointed out in the FNH group. Parameters of sensitivity, specificity, PPV, NPV and efficacy for the given radiological features differentiating FNH and for the set of these features including clinical data such as lack of liver cirrhosis were counted.

The research was approved by Independent Bioethic Committee for Scientific Study of Medical University of Gdansk and patients gave their written informed consent to participate.

For evaluation, program Statistica 8 (StatSoft Inc, Tulsa, OK, USA) and $\chi^2$ test were used.
Results

Interobserver reproducibility for all the parameters was high with high kappa values. The agreement among observers was almost perfect for all the parameters with values 0.8-1.0.

Most patients with FNH were females (31 out of 39 subjects) in contrast to the non-FNH group (62 out of 119 subjects) - difference statistically significant, p<0.05. There was also a statistically significant difference concerning the patients' medium age - subjects in the FNH group were significantly younger (36 years of age) as compared to the non-FNH group (56 years of age) - difference statistically significant, p<0.05.

Medium size of a focus and median value in the FNH group was 29 mm, while in the non-FNH group - 20 mm.

Radiological features appearing statistically more often in FNH than in other focal changes on MRI are as following:

1. homogenous enhancement in hepatic arterial phase (stated in 40 foci with FNH) - Fig.1 on page 9,
2. presence of a central scar (stated in 30 patients with FNH and 1 patient with fibrolamellar carcinoma) - Fig. 1 on page 9,
3. enhancement similar to that in the liver in portal venous phase and equilibrium phase (stated in 39 patients with FNH and 89 with other lesions and respectively in 44 and in 273 cases),
4. enhancement similar to that in the liver or hyperintensive in comparison to the liver parenchyma in hepatocyte-selective phase - Fig. 2 on page 9,
5. intensity similar to that of the liver on T1 and T2-weighted images - Fig. 3 on page 10 - 4 on page 11.

Their diagnostic efficacy is presented in table 1.

Satisfactory differentiation characteristic distinguishing FNH from other lesions was attributed to the presence of a central scar evaluated in 70% on MRI examination (efficacy on the level of 96%).

Other feature with high parameters of diagnostic efficacy (about 85%), assessed on MRI examinations (table 1) is homogenous enhancement in the arterial phase; however, low PPV value (33%) strongly decreases its clinical usefulness.

A feature characterized by highest values of sensitivity and specificity in the diagnosis of FNH was enhancement of a lesion in the hepatocytic phase - isointense or hyperintense focus (sensitivity - 100%, specificity - 94%). FNH was isointense or hyperintense with respect to the normal liver parenchyma in the hepatobiliary phase in all the cases. Because the same enhancement as FNH (isointensive) in the hepatocytic phase was
stated in 19 HCC foci, calculated PPV value of the MRI examination in the diagnosis of
FNH after use of organ-specific media is 69% and is not sufficient to decide to observe
patients with suspected FNH foci. This fact encouraged the authors to conduct a multi-
factorial analysis which took into account how many and what kind of radiological features
a tumor must have to be diagnosed with certainty as FNH (table 2).

Sum of two radiological symptoms (enhancement pattern non-hypointensive in the
hepatobiliary phase and homogeneous enhancement in the hepatic arterial phase) as a
criterion enabling diagnosis of FNH is characterized by high values of PPV coefficient
(82% - only 9 HCC foci were isointensive in the hepatic phase and at the same time
showed homogenous enhancement in the HAP phase) and other indexes of diagnostic
efficacy (91-99%), what is presented in table 2.

Further analysis was based on radiological features (the mentioned above sum of two
radiological symptoms) and clinical data, assuming that patients with chronic liver disease
are ruled out of the group with FNH. If a patient does not suffer from liver cirrhosis and has
a hepatic focus which is characterized by intensive enhancement in the arterial phase
and non-hypointensive (iso- or hyperintensive) in the hepatocytic phase
(Fig. 5-8), probability of FNH presence is close to certainty (98%) and indexes of
diagnostic efficacy of such method equal 98-100% (table 2).

Table 1. Diagnostic efficiency of MR radiological findings.

<table>
<thead>
<tr>
<th>radiological findings</th>
<th>sensitivity</th>
<th>specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>isointensive in T1w</td>
<td>0.55</td>
<td>0.16</td>
<td>0.08</td>
<td>0.74</td>
<td>0.20</td>
</tr>
<tr>
<td>isointensive in T2w</td>
<td>0.86</td>
<td>0.79</td>
<td>0.35</td>
<td>0.98</td>
<td>0.80</td>
</tr>
<tr>
<td>non-hypointensive focus in CMD</td>
<td>1.00</td>
<td>0.94</td>
<td>0.69</td>
<td>1.00</td>
<td>0.95</td>
</tr>
<tr>
<td>central scar</td>
<td>0.70</td>
<td>0.99</td>
<td>0.97</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>homogeneous enhancement in HAP</td>
<td>0.85</td>
<td>0.84</td>
<td>0.33</td>
<td>0.98</td>
<td>0.84</td>
</tr>
<tr>
<td>isointensive to liver</td>
<td>0.84</td>
<td>0.75</td>
<td>0.30</td>
<td>0.97</td>
<td>0.76</td>
</tr>
<tr>
<td>non-hypointensive focus in CMD</td>
<td>sensitivity</td>
<td>specificity</td>
<td>PPV</td>
<td>NPV</td>
<td>accuracy</td>
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</tr>
<tr>
<td>homogeneous enhancement in HAP</td>
<td>0.91</td>
<td>0.97</td>
<td>0.82</td>
<td>0.99</td>
<td>0.97</td>
</tr>
<tr>
<td>homogeneous enhancement in HAP</td>
<td>0.98</td>
<td>1.00</td>
<td>0.98</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>no cirrhosis</td>
<td>0.64</td>
<td>1.00</td>
<td>1.00</td>
<td>0.95</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic efficiency of logical sum of MR radiological findings.
| focus in CMD central scar | homogeneous enhancement in HAP non-hypointensive focus in CMD central scar isointensive in T2w | homogeneous enhancement in HAP non-hypointensive focus in CMD central scar isointensive in T2w isointensive to liver enhancement in EP | 0.58 | 1.00 | 1.00 | 0.94 | 0.95 |
Fig. 0: MR image of FNH in segment IVB of left lobe in the liver. Hepatic arterial phase scan shows typical enhancement pattern of FNH - intensive homogenous enhancement and hypodense central scar.

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**Fig. 0:** The same lesion as in Fig.1. Hepatocyte-selective phase confirms diagnosis of FNH presenting higher enhancement of FNH than surrounding liver parenchyma.

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**Fig. 0:** The same lesion as in Fig.1-2. The lesion is isointensive to the liver parenchyma in T1-weighted image.

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Fig. 0: The same lesion as in Fig.1-3. The lesion is isointensive to the liver parenchyma in T2-weighted image.

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Fig. 0: MR image of FNH in segment V occurring in a patient without liver cirrhosis. The lesion is hypointense in T1-weighted image.

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**Fig. 0:** The same lesion as in Fig.5. The lesion is isointense in T2-weighted image.

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Fig. 0: The same lesion as in Fig.5-7. Hepatocyte-selective phase shows similar enhancement of FNH to surrounding liver parenchyma.

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**Fig. 0:** The same lesion as in Fig.5-6. Hepatic arterial phase scan presents homogenous enhancement of FNH with small central scar.

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Conclusion

At present, the best diagnostic tool is combination of a dynamic MR-examination and hepatobiliary phase of Gd-BOPTA. The only limitation of this method is presence of tiny foci of HCC, non-hypointense in the hepatocytic phase and strongly enhancing after CM administration in the arterial phase. This limitation can be avoided thanks to a good cooperation between a clinician and radiologist, excluding FNH patients with liver cirrhosis or other liver chronic disease.

Summarizing, MRI examination with administration of hepatotropic contrast media is effective method in differential diagnosis of FNH. Hepatotropic compounds enable to assess not only vascularization of focal changes but also hepatocyte function in the course of one examination (extracellular phase and liver specific study in one stop-shop-examination).
References

Personal Information

E. Szurowska¹ eszurowska@gumed.edu.pl

J. M. Pienkowska¹

T. Nowicki¹,

E. Izycka-Swieszewska²

K. Markiet³

D. Zadrożny⁴

M. Studniarek¹

1. Department of Radiology, Medical University of Gdansk, 80-211 Gdansk, Debinki 7, Poland, tel/fax: +48583492260
2. Department of Pathomorphology, Medical University of Gdansk, Gdansk, Poland
3. Department of Neonatal, Gynecological and Urological Radiology, Medical University of Gdansk, Gdansk, Poland
4. Department of General Surgery and Transplantation, Medical University of Gdansk, Gdansk, Poland