Manifestations of Hepatic Focal Nodular Hyperplasia in Hepatobiliary Phase of Enhancement by Hepatocyte-specific Contrast Agent: Comparison With Pathologic Findings

Jiangfeng Xu

Department of Radiology, Shulan Hangzhou Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, Hangzhou

Liqing Zhang

Department of Radiology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou

Jianxun Li

Department of Radiology, Shulan Hangzhou Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, Hangzhou

Xiaojian Cui

Department of Radiology, Jinhua People's Hospital, Jinhua

Qingping Jiang (✉ hzsyyyj2020@sina.com)

Department of Radiology, Shulan Hangzhou Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, Hangzhou

Yan Zhang

Department of Radiology, Shulan Hangzhou Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, Hangzhou

Research Article

Keywords: focal nodular hyperplasia, Gd-EOB-DTPA, hepatobiliary phase, β -catenin

Posted Date: September 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-870839/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: To explore the signals and diagnostic value of hepatic focal nodular hyperplasia (FNH) in the hepatobiliary phase of gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid (Gd-EOB-DTPA) enhanced MRI.

Methods: Imaging data of 43 pathologically proven FNH lesions from 39 patients who underwent Gd-EOB-DTPA enhanced MRI scanning at our hospital between January 2016 and June 2019 were retrospectively analyzed. The signal characteristics in the hepatobiliary phase were analyzed and compared with the pathologic findings.

Results: According to the characteristics of signals in the hepatobiliary phase, the signals were classified as follows: homogenous iso-high intensity signals in 20.93% (9/43) lesions, heterogeneous iso-high intensity signals in 67.44% (29/43) lesions, homogenous low-intensity signals in 4.65% (2/43) lesions, and heterogeneous low-intensity signals in 6.98% (3/43) lesions. Two patients were with multiple lesions, where one was with 2 lesions of heterogeneous high-intensity signals, and the other with 3 lesions of heterogeneous low-intensity signals. Pathologic findings were as follows: the slices of the 38 lesions with high-intensity signals in a hepatobiliary phase were with hyperplastic hepatocytes, inflammatory cell infiltration, and malformed blood vessels. Twenty-nine of the lesions were with fiber tissues of different degrees and were classified as classic type. The remaining 9 lesions were without fibrous scars and were classified as non-classic type. The other 5 of the 43 lesions were non-classic FNH with no evident fibrous tissues, while 4 of them were with >40% steatosis in the hyperplastic hepatocytes; the immunohistochemistry showed CK7(-)/CK19(-) in 1 lesion and β -catenin (nucleus +) in another lesion. Comparisons of pathologic with imaging findings were as follows: twenty-nine lesions were with heterogeneous iso-high intensity signals, of which the slices showed evident fibrous tissues of different degrees, and the slices of 9 lesions with homogenous iso-high intensity signals in the hepatobiliary phase showed no fibrous tissues. Three lesions with heterogeneous low-intensity signals in the hepatobiliary phase showed about 80% mixed steatosis in hyperplastic hepatocytes. The other two lesions both showed homogeneous low-intensity signals in the hepatobiliary phase, where 1 lesion was with >40% macrovesicular steatosis and CK7/CK19 (-), while the other only showed β -catenin (nucleus +) by immunohistochemistry.

Conclusions: The signals of FNH in the hepatobiliary phase showed various characteristics, where the signal differences were mainly associated with the number of hyperplastic hepatocytes in lesions, presence of steatosis, fibrous scars, and conditions of small bile ducts, and potentially associated with β -catenin (nucleus+). Low-intensity signals were relatively rare for FNH, thus representing a relatively major challenge for diagnosing this type FNH.

Background

Hepatic focal nodular hyperplasia (FNH), which accounts for about 8% of all primary liver tumors, is a lesion composed of benign hepatocyte hyperplasia, with normal or almost normal tissue structures [1–6]. Most researchers suggest that FNH is secondary to congenital hepatic vascular malformation or caused by adaptive vascular injuries [7–10]. A clear diagnosis of FNH could help to avoid unnecessary invasive examinations or surgery. Gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid (Gd-EOB-DTPA; trade name: primovist) is a hepatocyte-specific contrast agent that normal hepatocytes can uptake [11]. FNH is characterized by iso- or high-intensity signals in the hepatobiliary phase, which has relatively important value in the diagnosis and differential diagnosis of this disease [12–14]. However, with the wide application of Gd-EOB-DTPA in clinical practice, several researchers have found that in addition to iso- and high-intensity signals, FNH can also show low-intensity signals in a hepatobiliary phase when the tissues in lesions changes [15–16]. Such non-classic manifestations have been identified as a substantial challenge for pre-operative diagnosis. In this study, 43 FNH lesions were retrospectively analyzed, and the signals in a hepatobiliary phase were classified and compared with pathologic findings. The goal of this study was to further investigate the association of FNH signal characteristics in the hepatobiliary phase with pathologic changes and provide additional evidence to help clinical diagnosis.

Methods

General characteristics

This retrospective study was approved by the Ethics Committee of the Shulan (Hangzhou) hospital. Clinical data of the 39 patients with pathologically proven FNH who received Gd-EOB-DTPA enhanced MRI at our hospital between January 2016, and June 2019 were collected.

The inclusion criteria were the following: patients with FNH proven by pathological examinations following surgery or biopsy. The exclusion criteria were: 1) patients who could not receive pathological examination due to severe cardiac diseases, pulmonary diseases, cerebral diseases, or tumors; 2) patients who were diagnosed with FNH only by imaging follow-up but whose condition was not proven by pathological examination.

Finally, 39 patients with 43 FNH, 31 males and 8 females were included in this study. The male-to-female ratio of the patients was 3.9:1. The age of the patients ranged from 33 to 72 years (50.7 ± 11.3 years).

Parameters and methods of MRI examination

MRI examination methods

End-expiratory hold or respiratory gating method was used for the MRI scanning, and patients did not ingest any water for 4 h before MRI scanning. Gd-EOB-DTPA (Primovist, Bayer Schering Pharma, Berlin, Germany) was used as the contrast agent. The dose of Gd-EOB-DTPA was 0.025 mmol/kg, and the

injection velocity was 2 ml/s; afterwards, 20 ml 0.9% NaCl solution was used to rinse the catheter with the velocity of 2 ml/s. After the intravenous injection of contrast agent, MRI scanning was performed at 18–23 s, 45–50 s, 90–120 s, and 15–20 min to acquire the images in arterial phase, portal venous phase, equilibrium phase, and hepatobiliary phase. The patients were required to hold their breath during the scanning.

Parameters for MRI scanning

GE Signa HDxt 1.5T MR apparatus (GE, Medical System; Milwaukee, USA) with abdominal 8-channel phased-array coil was used for scanning. The scanning sequences were as follows: 1) Cor FIESTA, TR 3.5ms, TE 1.5ms, slice thickness 7.0 mm, slice gap 9.0 mm, matrix 224×224, 1 excitation, and acquisition time 17 s; 2) Ax T2FRFSE RTrFatSAT, TE 90.2 ms, slice thickness 6.0 mm, slice gap 8.0 mm, matrix 320×196, 3 excitations, and acquisition time 2 min29s; 3) Ax DWI, b value = 800 mm/s, TR 10588.2 ms, TE 70 ms, slice thickness 6.0 mm, slice gap 8.0 mm, matrix 128×128, and acquisition time 1min 34s; 4) Ax LAVA + C (including masking plain scanning), TR 4.2 ms, TE 2.0 ms, slice thickness 5.0mm, slice gap 2.5 mm, matrix 320×224, and acquisition time 14 s; 5) Cor LAVA + C, TR 3.5 ms, TE1.7 ms, slice thickness 5.0 mm, slice gap 2.5 mm, matrix 320×224, and acquisition time 16 s; 6) BHAX3DDualEcho (positive/negative phase), TR 6.1 ms, TE 2.1 ms, slice thickness 5.2 mm, slice gap 2.6 mm, matrix 256x160, and acquisition time 15 s. Parameters for the scanning in a hepatobiliary phase were following: 1) parameters for Ax LAVA + C1 were identical to Ax LAVA + C; and 2) parameters for Cor LAVA + C1 were identical to Cor LAVA.

Methods of imaging examination and pathological diagnosis

The MRI images of all the patients were input to PACS, which were independently reviewed in a double-blind manner by two radiologists with the professional title of associate chief or higher and with more than ten years of experience in MRI diagnosis of liver diseases. Any disagreements were solved by discussion. The manifestations of FNH signals in the hepatobiliary phase (contrast to liver tissue background) were investigated, and after the reports of previous literatures were also considered, these signals in a hepatobiliary phase were classified into four types: 1) homogenous iso-high intensity signal; 2) heterogeneous iso-high intensity signal, 3) homogenous low-intensity signal, and 4) heterogeneous low-intensity signal.

According to the EASL Clinical Practice Guidelines that were issued in 2016 and the histological classification criteria developed by Nguyen et al. in 1999 [6, 17], two pathologists with the professional title of associate chief or higher analyzed the FNH specimens obtained by surgery or biopsy and then classified them into classic or non-classic FNH. Any disagreements were solved by discussion.

Statistical analysis

SPSS 25.0 software was used for the statistical analysis of data. Quantitative data in normal distribution were analyzed by *t*-test, and qualitative data were analyzed by χ^2 test. A P value < 0.05 was considered to be statistically significant.

Results

Characteristics and types of FNH signals in the hepatobiliary phase

The signals of the 43 FNH in hepatobiliary phase were as follows: 1) homogenous iso-high intensity signals in 9 FNH (20.93%); 2) heterogeneous iso-high intensity signals in 29 FNH (67.44%); 3) homogenous low-intensity signals in 2 FNH (4.65%); 4) heterogeneous low-intensity signals in 3 FNH (6.98%)(Table 1).

Table 1
Signals of FNH in the hepatobiliary phase

	n	Percentage
Homogenous iso-high intensity signal	9(9)	20.93%
Heterogeneous iso-high intensity signal	29(27)	67.44%
Homogeneous low-intensity signal	2(2)	4.65%
Heterogeneous low-intensity signal	3(1)	6.98%

Manifestations of plain and enhanced MRI images of FNH with signals in hepatobiliary phase of 4 different characteristics

Thirty-eight FNH were with iso-intensity signals in hepatobiliary phase, of which the T1WI showed 37 with iso-low intensity (Fig. 1a), and 1 with the high-intensity signal; T2WI showed 37 FNH were with iso- or slightly high-intensity signals (Fig. 1b), 1 with the high-intensity signal; DWI showed 36 FNH were with iso- or slightly high- intensity signals (Fig. 1c), and 2 with high-intensity signals. No evident attenuation was found on the in/out phases (Fig. 1d-e). These FNH showed high-intensity signals in the arterial phase and portal venous phase and iso-high intensity signals in the equilibrium phase (Fig. 1f-h). Twenty-nine of the lesions were with scars. Five FNH were with low-intensity signals in the hepatobiliary phase, among which the multiple lesions in 1 patient revealed evident signal attenuation on the in/out phase (Fig. 2d-e), slightly high-intensity signals on T2WI images (Fig. 2b), slightly high-intensity signals on DWI images (Fig. 2c), no evident envelop or scar, slightly low-intensity signals on T1WI (fat-saturated) images (Fig. 2a), and heterogeneous slightly low-intensity signals in the three phases during enhancement (Fig. 2f-h). One single FNH showed slightly high-intensity signal on T1WI image (Fig. 3a), high-intensity signal on T2WI image (Fig. 3b), high-intensity signal on DWI image (Fig. 3c), slight signal attenuation on in/out phase, and evident heterogeneous enhancements in the three phases (Fig. 3f-h). The other single FNH

showed slightly low-intensity signal on T1WI image (Fig. 4a), high-intensity on T2WI image (Fig. 4b), the high-intensity signal on DWI image (Fig. 4c), no signal attenuation on in/out phase (Fig. 4d-e), and slightly heterogeneous enhancements in the three phases (Fig. 4f-h). Slight signal reduction in the equilibrium phase was found, while no scar or envelope was observed. The lesion was with a low-intensity signal in the hepatobiliary phase and was misdiagnosed as hepatocellular carcinoma.

Pathological features of FNH with signals of different characteristics in the hepatobiliary phase

Among all the 43 lesions that were proven by pathological examinations of specimens from surgery or biopsy, 38 lesions showed iso-high intensity signals in the hepatobiliary phase, 29 lesions (76.32%; 29/38) were classic pathologic type, and 9 lesions (23.68%; 9/38) were with non-classic type. Five lesions showed low-intensity signals in the hepatobiliary phase, while the pathological examinations revealed that all of these lesions were non-classic type. Statistical analysis showed that the pathologic types of FNH with iso-high and low-intensity signals in the hepatobiliary phase significantly differed ($P < 0.05$). All the FNH with low-intensity signals in a hepatobiliary phase were non-classic types (Table 3), among which the gross observations showed a gray-yellow mass with a clear boundary and different sizes, with the color that was similar to adjacent liver tissues, moderate texture, and nodular shapes. The smaller the lesions were, the more unclear the scars and nodular shapes were. Microscopic examination (Table 2) showed that 29 (29/43; 67.44%) FNH were non-classic types, for which the examinations of slices showed hepatocyte hyperplasia, fibrous tissues, infiltration of inflammatory cells, and malformed blood vessels (Fig. 1j). Fourteen (14/43; 32.56%) FNH were non-classic types, among which 9 were with no fibrous scars; 3 FNH were with no fibrous scars but with 80% mixed steatosis and slight hepatocyte atypia (Fig. 2j); 1 FNH was without fibrous scars but with 40% macrovesicular steatosis, while immunohistochemistry showed CK7(-)CK19(-)(Fig. 3j, Table 2). The other FNH was misdiagnosed as hepatocellular carcinoma according to imaging frozen section examination results, for which the regular pathologic examination showed non-classic type, immunohistochemistry showed Glypican-3 (-), AFP (-), β -catenin (nucleus +), CD10 (-), Hepatocyte (+), CD34 (-), CK7 (focal +), CK19 (focal +), Ki67 (+ 3%), P53 (-), HMB45 (-), MelanA (-), and S100 (-)(Fig. 4j).

Table 2
Pathologic characteristics of the 39 FNH*

		n	Total number (percentage)
Classic FNH		29	29(67.44%)
Non-classic FNH	CK7(-)CK19(-)	1	14 (32.56%)
	Steatosis (> 40%) (low-intensity signal in hepatobiliary phase)	4	
	No scar	9	
	β -catenin (nucleus +)	1	
	With hepatocyte atypia (low-intensity signal in hepatobiliary phase)	1	
*One non-classic FNH can show two different non-classic pathologic manifestations			

Table 3
Pathologic types of FNH with iso-high intensity or low-intensity signals in the hepatobiliary phase

	FNH of iso-high intensity signals	FNH of low-intensity signals	Pvalue
Classic	29(76.32%)	0	0.003
Non-classic	9(23.68%)	5(100%)	

In this study, immune labeling of β -catenin was performed in 21 lesions (Table 4). Fourteen FNH (including 11 with iso-high intensity signals and 3 with low-intensity signals in hepatobiliary phase) were β -catenin (-), 6 FNH (including 5 with iso-high intensity signals and 1 with low-intensity signals in hepatobiliary phase) were β -catenin (membrane +), and 1 (with low-intensity signals in a hepatobiliary phase that was misdiagnosed as HCC) was β -catenin (nucleus +).

Table 4
 β catenin expression in FNH with different intensities of signals in hepatobiliary phase by immunohistochemistry

	β -catenin(-)	β -catenin (membrane +)	β -catenin (nucleus +)
Iso-high intensity signal	11	5	0
Low-intensity signal	3	1	1

Discussion

FNH is the benign hyperplastic lesion of the liver. Numerous studies have demonstrated that the diagnostic accuracy of Gd-EOB-DTPA enhanced MRI is higher than 90% [18–22], where the characteristic manifestation is the iso-intensity signal in the hepatobiliary phase. Still, with the wide application of Gd-EOB-DTPA, we found that some FNH can also show low-intensity signal in the hepatobiliary phase [15–16], which may cause difficulties for radiologists when making the diagnosis.

Mechanisms underlying the effects of Gd-EOB-DTPA on FNH

Gd-EOB-DTPA possesses the characteristic of both non-specific extracellular and hepatocyte-specific contrast agents. On the one hand, Gd-EOB-DTPA can be used as the non-specific extracellular contrast agent to attain the regular enhancement similar to Gd-DTPA enhanced scanning; on the other hand, Gd-EOB-DTPA can also be used as the hepatocyte-specific contrast agent in the scanning. When delayed for about 15–20 min after venous injection, about 50% Gd-EOB-DTPA could be transferred into hepatocytes from extracellular space through the ATP-dependent organic anion transporting polypeptide 8 (OATP8) on the sinus wall of the hepatocyte, which is then excreted into cholangiole by the multidrug-resistant protein carriers on the surface of cholangiole [23–24]. The uptake of Gd-EOB-DTPA by hepatocytes is dependent on the expression level of OATP8 [24–25]. The other 50% Gd-EOB-DTPA are excreted by the kidney [23]. As FNH also contains hepatocytes of normal functions and thus can uptake the contrast agent, the FNH lesion can show iso- or high-intensity signals in the hepatobiliary phase, compared with the surrounding liver parenchyma.

Manifestations of FNH signals in hepatobiliary phase and the corresponding pathologic fundament

FNH with iso-high intensity signal in hepatobiliary phase and the pathologic fundament

In this study, 38 FNH with iso-high intensity signals in the hepatobiliary phase from 36 patients were analyzed, which accounted for 88.37% (38/43) of all the FNH. Among these lesions, 67.44% were with heterogeneous iso-high intensity signal, and 20.93% were with homogeneous iso-high intensity signal. The pathologic examination of the 38 FNH showed that all lesions contained normally hyperplastic hepatocyte nodules, inflammatory cells, and angiogenesis. Immunohistochemistry showed that all the lesions were hepatocyte (+), AFP (-), CD4 (lymphocyte +), CD8 (lymphocyte +), CD34 (capillary proliferation), CK7 (+), and CK19 (+). Twenty-nine of the lesions contained different degrees of fibrous tissues, the manifestations in the hepatobiliary phase showed heterogeneous thin-ring or thick ring-shaped iso-high intensity signals, and the pathologic examinations showed classic type. The other nine lesions were non-classic types without fibrous scars and showed nodular homogeneous high-intensity

signals in the hepatobiliary phase. In this study, the pathologic difference between the lesions with homogeneous or heterogeneous iso-high intensity signals in the hepatobiliary phase was the presence of central or eccentric fibrous septum, as the fibrous septal scars are similar to the portal area, in which OATP8 is not expressed by hepatocytes [26]. Since the peripheral hepatocyte nodules can normally express OATP8 or even over it, FNH can be manifested as low-intensity signals surrounded by peripheral iso- or high-intensity signals in the hepatobiliary phase, thus showing the overall heterogeneous or iso-high intensity signals. In FNH lesions for which the pathologic examinations showed no fibrous scars, homogeneous iso- or high-intensity signals could be detected in the hepatobiliary phase. The comparison of the signal characteristics of FNH in the hepatobiliary phase with pathologic examination results showed that the signals of FNH in the hepatobiliary phase were closely associated with the histological features of lesions. Specifically, the signals were associated with the number of normally hyperplastic hepatocytes and fibrous scars.

FNH with low-intensity signal in hepatobiliary phase and the pathologic fundament

In this study, 5 FNH from 3 patients were with low-intensity signals in the hepatobiliary phase, of which some 4.65% were with homogeneous low-intensity signal and 6.98% with heterogeneous low-intensity signal in the hepatobiliary phase. This was generally consistent with previous studies reporting 3–8% incidence for FNH with low-intensity signals in the hepatobiliary phase [15]. Kessel *et al.* [16] and Cannella *et al.* [27] have already reported on the case of FNH with low-intensity signal in the hepatobiliary phase, where the case reported by Kessel *et al.* showed the pathologic findings of fibrous tissues throughout the lesion, while the case reported by Van et al. showed evident attenuation in in/out phase, which indicated the existence of steatosis, and the lesion showed low-intensity signal in hepatobiliary phase. In this study, 5 FNH were found with low-intensity signal in the hepatobiliary phase, of which four lesions showed different degrees of steatosis in in/out phase. One patient (3 lesions) was with 80% mixed steatosis in the multiple lesions; one patient was with a single lesion and mixed steatosis that was dominant by $\geq 40\%$ macrovesicular steatosis. Ding *et al.* [28] reported that steatosis of hepatocytes could reduce the functions of hepatocytes, thus speculating that steatosis of hepatocytes in FNH could lead to the reduced uptake of Gd-EOB-DTPA, eventually resulting in the low-intensity signal. One patient (3 lesions) with multiple lesions showed slight atypia of part of hepatocytes in addition to 80% mixed steatosis. Although it is believed that FNH usually does not undergo malignant transformation, several researchers have already reported cases with malignant transformation of FNH [29]. The reduced hepatocytes could also reduce the uptake of hepatocyte-specific contrast agents by lesions. Our results showed that atypia of hepatocytes could also be one of the causes influencing the changes of signals of FNH in the hepatobiliary phase. The pathologic examination of the patient with a single lesion showed the FNH was with 40% mixed steatosis, and the immunohistochemistry showed CK7/CK19(-). Cannella *et al.* [27] analyzed the effects of CK7 and CK19 on the changes of FNH signals in hepatobiliary phase, reporting that the number, types, and distribution of bile ducts all influenced the signal changes of FNH in hepatobiliary phase. Therefore, we speculated that the low-intensity signal of FNH in the hepatobiliary could be caused by steatosis of hepatocytes and negativity of CK7 and CK19. The other patient with a

single lesion was misdiagnosed with HCC based on imaging and frozen pathologic examinations. Nevertheless, this patient was finally diagnosed as non-classic FNH by routine pathologic examination. No evident fibrous tissues were found in the slice of the lesion, and only 5% steatosis was found. Immunohistochemistry showed β -catenin (nucleus +) in the lesion; however, the causes of low-intensity signal in the hepatobiliary phase have still not been clarified. Previous studies have not reported on the activation mutation of β -catenin in FNH. β -catenin mainly shows strip-shaped expression in FNH, which is different from catenin-activated HCA or diffused cytoplasmic GS staining and nuclear β -catenin staining in liver cancer [30]. In this study, one patient with the hepatobiliary phase was misdiagnosed with liver cancer, which showed β -catenin (nucleus +). We speculated this could be associated with gene mutation, inhibition of the Wnt/ β -catenin pathway, and low expression of OATP1B3.

After analyzing the low-intensity signals of FNH in the hepatobiliary phase and the pathology, we speculated that the pathologic fundamentals could be as follows: 1) Steatosis: when there is steatosis in a certain proportion of hyperplastic hepatocytes in FNH lesion, functions of hepatocytes are reduced. In such cases, the expression of OATP8 could also be reduced, thus causing FNH to show homogeneous or heterogeneous low-intensity signals in the hepatobiliary phase; 2) formation of fibrous scars: if the fibrous tissues were throughout the lesion, the FNH does not uptake the specific contrast agent, thus showing low-intensity signal in hepatobiliary phase; 3) atypia of hepatocytes: the reduction of normal hepatocytes in FNH lesion can lead to the reduced uptake of specific contrast agent, thus showing low-intensity signal in hepatobiliary phase; 4) types of bile ducts: previous studies [27, 31] have shown that there are three types of bile ducts in FNH, namely the bile ducts similar to surrounding liver tissues, hyperplastic bile ducts, and metaplastic bile ducts. The former two types, which are with relatively high differentiation levels, can uptake and excrete Gd-EOB-DTPA and can explain the high-intensity signals in hepatocytes, while the latter type is with relatively poor function and can poorly communicate to small bile ducts, thus explaining the low-intensity signal in hepatobiliary phase; 5) β -catenin mutation: we speculated that very few lesions are with β -catenin (nucleus +) mutation, the suppression of Wnt/ β -catenin pathway and low expression of OATP1B3 could lead to low-intensity signal in hepatobiliary phase.

The present study has the following limitations. First, the number of FNH with low-intensity signals in the hepatobiliary phase was small, and more multi-center studies with a larger sample are needed to further investigate the reasons and underlying mechanisms of low-intensity signals of FNH in the hepatocellular phase. In addition, this was a retrospective study, and selection bias could not be avoided.

Conclusions

In summary, FNH shows various manifestations in the hepatobiliary phase, where imaging manifestations vary according to the number and function of hyperplastic hepatocytes and are associated with the degree and type of steatosis of hepatocytes, number of fibrous scars, hepatocyte atypia, number and types of bile ducts, and mutation of a β -catenin gene by immunohistochemistry. There are great challenges in the pre-operative diagnosis of FNH with low-intensity signals in the

hepatobiliary phase. Comprehensive analysis of the clinical and imaging data and follow-up analysis or biopsy could help to reduce the number of unnecessary surgeries.

Abbreviations

FNH: Focal nodular hyperplasia; Gd-EOB-DTPA: Gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid; PACS: Picture Archiving and Communication Systems.

Declarations

Ethics approval and consent to participate

Approval was obtained by the Ethics Committee of the Shulan (Hangzhou) hospital. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This study is a retrospective analysis, it did not include any human trial.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Authors have no conflict of interest to declare.

Funding

This work was funded by Medical Science Research Program of Zhejiang Province (2020KY692, 2021KY861) and Chinese Medical Science Research Program of Zhejiang Province (2021ZQ072).

Authors' contributions

JFX and LQZ carried out the studies, participated in collecting data, and drafted the manuscript. JXL prepared figures 1-4 and tables. XJC and YZ performed the statistical analysis and participated in its design. QPJ helped to draft the manuscript. All authors read and approved the final manuscript.

References

1. Rui Xu, Jing Wang, Xiaoyu Huang, Qiaoying Zhang, Yijing Xie, Lan Pang, et al. Clinical value of spectral CT imaging combined with AFP in identifying liver cancer and hepatic focal nodular hyperplasia. JBUON. 2019; 24(4): 1429-1434.
2. Chen Xiangguang, Yang Zhiqi, Deng Junliang. Use of 64-Slice Spiral CT Examinations for Hepatocellular Carcinoma (DR LU) . JBUON. 2019; 24(4): 1435-1440.
3. Joseph F Buell, Hadrien Tranchart, Robert Cannon, Ibrahim Dagher. Management of benign hepatic tumors. The Surgical clinics of North America. 2010; 90(4): 719-735.
4. Kamal G, Ishak, Zachary D. Goodman, J. Thomas Stocker. Tumors of the Liver and Intrahepatic Bile Ducts. Atlas of Tumor Pathology Third. 2002; 40(2):199-199.
5. Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy 2nd PF. Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. Gastroenterology. 1983; 84(5): 994-1002.
6. Nguyen BN, Jeanfrançois Fléjou, Terris B, Belghiti J, Degott C. Focal Nodular Hyperplasia of the Liver: A Comprehensive Pathologic Study of 305 Lesions and Recognition of New Histologic Forms. American Journal of Surgical Pathology. 1999; 23(12):1441-1454.
7. Kondo F, Nagao T, Sato T, Tomizawa M, Kondo Y, Matsuzaki O, et al. Etiological analysis of focal nodular hyperplasia of the liver, with emphasis on similar abnormal vasculatures to nodular regenerative hyperplasia and idiopathic portal hypertension. Pathology-Research and Practice. 1998; 194(7): 487-495.
8. Wanless IR, Mawdsley C, Adams R. On the pathogenesis of focal nodular hyperplasia of the liver. Hepatology. 1985; 5(6): 1194-1200.
9. Kondo F. Benign nodular hepatocellular lesions caused by abnormal hepatic circulation: etiological analysis and introduction of a new concept. Journal of gastroenterology and hepatology. 2001; 16(12):1319-1328.
10. Patacsil Stephen J, Noor Muhammad, Leyva Alexander. A Review of Benign Hepatic Tumors and Their Imaging Characteristics .Cureus. 2020; 12(1): e6813.
11. Fujita Nobuhiro, Nishie Akihiro, Asayama Yoshiki, Ishigami Kousei, Ushijima Yasuhiro, Kakihara Daisuke, et al. Hyperintense Liver Masses at Hepatobiliary Phase Gadoteric Acid-enhanced MRI: Imaging Appearances and Clinical Importance .Radiographics. 2020; 40(1): 72-94.
12. Suh CH, Kim KW, Kim GY, Shin YM, Kim PN, Park SH. The diagnostic value of Gd-EOB-DTPA-MRI for the diagnosis of focal nodular hyperplasia: a systematic review and meta-analysis. European Radiology. 2015; 25(4): 950-960.
13. Gupta RT, Iseman CM, Leyendecker JR, Shyknevsky I, Merkle EM, Taouli B. Diagnosis of Focal Nodular Hyperplasia With MRI: Multicenter Retrospective Study Comparing Gadobenate Dimeglumine to Gadoterate Disodium. American Journal of Roentgenology. 2012; 199(1): 35-43.
14. Grazioli L, Morana G, Kirchin M A, Schneider G. Accurate Differentiation of Focal Nodular Hyperplasia from Hepatic Adenoma at Gadobenate Dimeglumine-enhanced MR Imaging: Prospective Study. Radiology. 2005; 236(1):166-177.

15. An HS, Park HS, Kim YJ, Jung SI, Jeon HJ. Focal nodular hyperplasia: characterisation at gadoxetic acid-enhanced MRI and diffusion-weighted MRI. *The British journal of radiology*. 2013; 86(1028):
16. Kessel CS, Boer E, Kate FJ, Brosen LA, Veldhuis WB, Leeuwen MS. Focal nodular hyperplasia: hepatobiliary enhancement patterns on gadoxetic-acid contrast-enhanced MRI. *Abdominal Imaging*. 2013; 38(3):490-501.
17. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the management of benign liver tumours. *J Hepatol*. 2016; 65(2): 386-398.
18. Kierans AS, Kang SK, Rosenkrantz AB. The Diagnostic Performance of Dynamic Contrast-enhanced MR Imaging for Detection of Small Hepatocellular Carcinoma Measuring Up to 2 cm: A Meta-Analysis. *Radiology*. 2016; 278(1):82-94.
19. Motosugi U, Ichikawa T, Morisaka H, Sou H, Muhi A, Kimura K, et al. Detection of Pancreatic Carcinoma and Liver Metastases with Gadoxetic Acid-enhanced MR Imaging: Comparison with Contrast-enhanced Multi-Detector Row CT. *Radiology*. 2011; 260(2):446-453
20. Martino MD, Marin D, Guerrisi A, Baski M, Galati F, Rossi M, et al. Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the detection of hepatocellular carcinoma in patients with cirrhosis. *Radiology*. 2010; 256(3):806-816.
21. Yoneda N, Matsui O, Kitao A, Kozaka K, Kobayashi S, Sasaki M, et al. Benign hepatocellular nodules: hepatobiliary phase of gadoxetic acid-enhanced MR imaging based on molecular background. *Radiographics*. 2016; 36(7): 2010-2027.
22. Zech CJ, Grazioli L, Breuer J, Reiser MF, Schoenberg SO. Diagnostic Performance and Description of Morphological Features of Focal Nodular Hyperplasia in Gd-EOB-DTPA-Enhanced Liver Magnetic Resonance Imaging: Results of a Multicenter Trial. *Investigative Radiology*. 2008; 43(7):504-511.
23. Jhaveri K, Cleary S, Audet P, Balaa F, Bhayana D, Burak K, et al. Consensus Statements From a Multidisciplinary Expert Panel on the Utilization and Application of a Liver-Specific MRI Contrast Agent (Gadoxetic Acid). *American Journal of Roentgenology*. 2015; 204(3):498-509.
24. Leonhardt M, Keiser M, Oswald S, Kuhn S, Jia J, Grube M, et al. Hepatic Uptake of the Magnetic Resonance Imaging Contrast Agent Gd-EOB-DTPA: Role of Human Organic Anion Transporters. *Drug Metabolism and Disposition*. 2010; 38(7):1024-1028.
25. Narita M, Hatano E, Arizono S, Miyagawa-Hayashino A, Isoda H, Kitamura K, et al. Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. *Journal of Gastroenterology*. 2009; 44(7): 793-798.
26. Fujiwara H, Sekine S, Onaya H, Shimada K, Mikata R, Arai Y. Ring-like enhancement of focal nodular hyperplasia with hepatobiliary-phase Gd-EOB-DTPA-enhanced magnetic resonance imaging: radiological-pathological correlation. *Japanese Journal of Radiology*. 2011; 29(10): 739-743
27. Cannella R, Rangaswamy B, Minervini MI, Borhani AA, Tsung A, Furlan A. Value of Texture Analysis on Gadoteric Acid-Enhanced MRI for Differentiating Hepatocellular Adenoma From Focal Nodular Hyperplasia . *AJR*. 2019; 212(3): 538-546.

28. Ying Ding, Mengsu Zeng, Shengxiang Rao, Caizhong Chen, Xiaofeng Zhou. Potential values for diagnosis and assessment of nonalcoholic fatty liver disease staging using Gd+-EOB-DTPA-enhanced MRI . Zhong Hua Gan Zang Bing Za Zhi. 2015; 23(2): 297-299.
29. Petsaa T, Tsamandas A, Tsota I, Karavias D, Karatza C, Vassiliou V, et al. A case of hepatocellular carcinoma arising within large focal nodular hyperplasia with review of the literature. World J Gastroenterol. 2006; 12(40): 6567-6571.
30. Bioulac-Sage P, Balabaud C, Bedossa P, Scoazec JY, Chiche L, Dhillon AP, et al. Pathological diagnosis of hepatocellular adenoma and focal nodular hyperplasia: Bordeaux update. J Hepatol. 2007; 46(3):521-527.
31. Slott P A, Liu M H, Tavoloni N. Origin, pattern, and mechanism of bile duct proliferation following biliary obstruction in the rat. Gastroenterology. 1990; 99(2): 466-477.

Figures

Figure 1

A 28-year-old male patient with a space-occupying lesion in the liver for 1 d. (a) T1WI image showed an iso-intensity signal of the lesion, and the central scar showed a low-intensity signal. (b) T2WI image showed a slightly high-intensity signal of the lesion, and the central scar showed a high-intensity signal. (c) DWI image showed a high-intensity signal of the lesion. (d, e) In/out phase showed no attenuation. (f) The image in the arterial phase showed a high-intensity signal of the lesion, and the central scar showed

a low-intensity signal. (g, h) Images in the portal venous phase and delayed phase showed slightly high-intensity signals of the lesion, and the central scar showed delayed enhancement. (i) Image in hepatobiliary phase showed petal-like high-intensity signals with uneven thickness, and the central scar showed a low-intensity signal. (j) Microscopy ($\times 100$) showed hyperplasia of fibrous tissue and infiltration of lymphocytes and plasmacytes in the fibrous septum, which separated the hepatocytes and formed nodules; hyperplasia of small bile ducts was also found.

Figure 2

A 26-year-old female patient with abnormal glutamyl transpeptidase level for 4 years. (a) T1WI image showed a slightly low-intensity signal of the lesion. (b) T2WI image showed a slightly high-intensity signal of the lesion. (c) DWI image showed a slightly high-intensity signal of the lesion. (d, e) In/out phase showed evident attenuation. (f) Image in the arterial phase showed that the enhancement was not substantial, and the lesion showed a slightly low-intensity signal. (g, h) Images in the portal venous phase and delayed phase showed slightly low-intensity signals of the lesion. (i) Image in hepatobiliary phase showed heterogeneous low-intensity signal. (j) Microscopy ($\times 100$): 3 stripes of liver tissues were obtained by biopsy of right liver, of which 5 portal areas were found, part of the liver lobule structures disappeared and were replaced by about 80% steatosis. Swelling of the residual hepatocytes, slight atypia of some hepatocytes that were accompanied by the thickening of hepatic trabecula, few capillaries with thick walls, and cholestasis were found. A low number of portal areas was found, and no abnormal changes were noticed.

Figure 3

A 31-year-old male patient with irregular liver morphology for over 1 month. (a) T1WI image showed a slightly low-intensity signal of the lesion. (b) T2WI image showed a slightly high-intensity signal of the lesion. (c) DWI image showed a slightly high-intensity signal of the lesion. (d, e) In/out phase showed evident attenuation. (f) Image in the arterial phase showed that the enhancement was not substantial, and the lesion showed a slightly low-intensity signal. (g, h) Images in the portal venous phase and delayed phase showed slightly low-intensity signals of the lesion. (i) Image in hepatobiliary phase showed heterogeneous low-intensity signal. (j) Microscopy ($\times 100$) (of liver tissues from the left lateral lobe of liver) showed non-classic focal nodular hyperplasia with the size of 9 cm*6 cm*5 cm. The examination of other liver tissues showed a small amount of inflammatory cell infiltration in the portal area and 40% steatosis (mainly macrovesicular steatosis).

Figure 4

A 61-year-old male patient hospitalized for liver mass for 6 d. (a) T1WI image showed a slightly low-intensity signal of the lesion. (b) T2WI image showed a slightly high-intensity signal of the lesion. (c) DWI image showed a slightly high-intensity signal of the lesion. (d, e) in/out phase showed evident attenuation. (f) Image in the arterial phase showed that the enhancement was not substantial, and the lesion showed a slightly low-intensity signal. (g, h) images in the portal venous phase and delayed phase showed slightly low-intensity signals of the lesion. (i) Image in hepatobiliary phase showed heterogeneous low-intensity signal. (j) Microscopy ($\times 100$) (of liver tissues from the left half liver) showed focal nodular hyperplasia with a diameter of 5 cm. The examination of the surrounding liver tissues showed a small amount of inflammatory cell infiltration in the portal area and focal steatosis (about 5%).