Article published online: 2021-07-30

Understanding the natural history of focal nodular hyperplasia in the liver with MRI

Jaydeep A Halankar, Tae Kyoung Kim, Hyun-Jung Jang, Korosh Khalili, Haider A Masoom

Department of Medical Imaging, University Health Network, Mount Sinai Hospital and Women's College Hospital, University of Toronto, Toronto, ON, Canada

Correspondence: Dr. Jaydeep Halankar, 1002, Silver Dunes, "C" wing, Tata Press Lane, Mumbai-400025, Maharashtra, India.
E-mail: jaydeep.halankar@gmail.com

Abstract

Aims: To determine the incidence of natural growth or regression of focal nodular hyperplasia (FNH) in the liver. **Material and Methods:** We retrospectively included 120 consecutive patients who were diagnosed to have FNH on MRI. The mean follow-up duration was 19 months (range: 6–64 months). There were 25 men and 95 women (age range: 18–80 years; mean: 45 years). There were 167 FNH lesions in the 120 patients. MRI images were retrospectively reviewed for interval growth or regression of FNH. The maximum size of the lesions was measured on axial arterial-phase images of the initial and the last MRI examinations. An interval increase or decrease in diameter of over 10% of the initial diameter was considered as positive growth or regression, respectively. The use of Oral contraceptives was also documented. **Results:** Interval growth was seen in 25/167 nodules (15%) over 7-48 months (mean: 21 months), with increase in size of 0.2-1.7 cm (mean: 0.6 cm) and percentage change of 10.5-340% (mean: 64%). Interval regression was seen in 13/167 (8%) of nodules over 7-63 months (mean: 22 months), with decrease in size of 0.2-0.9 cm (mean: 0.5 cm) and percentage change of 10.4-60% (mean: 24%).Five of 17 (29%) female patients with growing FNH and 25/78 (32%) female patients with non-growing FNH had a history of intake of oral contraceptives (P=0.83). **Conclusions:** Although FNH is benign and of no clinical significance, a substantial percentage of FNH shows interval growth or regression on long-term follow-up with MRI.

Key words: Liver; focal nodular hyperplasia; interval change; MRI

Introduction

Focal nodular hyperplasia (FNH) is a proliferation of normal non-neoplastic hepatocytes that is believed to be a local hyperplastic response to a vascular abnormality.[1] FNH is asymptomatic in most patients and in such cases no treatment is necessary. Therefore, an accurate differentiation of FNH from other significant focal liver masses is important.

Imaging diagnosis of FNH has rapidly improved with the introduction of multi-modality imaging techniques such as MRI,[2-3] contrast-enhanced USG,[4-5] and CT scan.[6] FNH, being a benign entity, can be confidently diagnosed with hepatobiliary-specific MRI examination. Most institutions do not biopsy FNH as the risks of the procedure outweigh the benefits. The use of a hepatobiliary-specific contrast agent for MRI studies has been reported to give very high specificity in differentiating FNH from hepatic adenomas by demonstrating the uptake of the hepatobiliary agent by FNH in the hepatobiliary-specific phase.[2]

Increase or decrease in the size of FNH during follow-up is reported to be rare. Mathieu *et al*,[7] in a 9-year study in 216 women with FNH, reported that a change in FNH size was seen in only 4 of 136 FNH (2.9%) cases, with size reduction in three cases and size increase in one case. In our experience, however, FNH with considerable interval size increase or decrease is more common than has been reported in prior studies.

Access this article online	
Quick Response Code:	Website: www.ijri.org
	DOI: 10.4103/0971-3026.101084

The purpose of this study is to determine the incidence of natural growth or regression of FNH in the liver.

Materials and Methods

Our institutional research ethics board approved this retrospective study and waived the need for patient consent.

We performed an electronic search of the radiology database using the keywords 'FNH,' 'MRI', and 'MultiHance' and identified 150 patients diagnosed to have FNH in the liver on gadobenatedimeglumine (MultiHance®, Bracco Imaging)-enhanced MRI over a 3-year period. Of these, 120 patients underwent two or more contrast-enhanced MRI scans performed at least six months apart and these patients were selected for inclusion in in this study. These 120 subjects included 25 men and 95 women in the age range of 18-80 years (mean: 45 years). All patients in our study were asymptomatic at initial diagnosis and remained symptom free throughout the follow-up period.

Of the 120 patients, 33 patients (28%) had more than one FNH nodule, and the remaining 87 patients (72%) had a single lesion. In cases with multiple lesions, we included up to four of the largest lesions in each patient. Mostly, all lesions had typical imaging characteristics for FNH on MultiHance® MRI. Thus, our final study sample included 167 FNH lesions in 120 patients. The interval between the first and last MRI examinations ranged from 6 to 64 months (mean: 19 months).

The diagnosis of FNH was made by histopathology in 9/120 (8%) patients. Diagnoses in the remaining 111 patients were confirmed by the characteristic MRI findings and the absence of risk factors for hepatocellular carcinoma (HCC). Typical signal intensity characteristics on T1W and T2W images (i.e., slightly hypointense or isointense to the normal liver on T1W images and slightly hyperintense or isointense to the normal liver on T2W images) [Figure 1A and B]; and marked enhancement in the arterial phase [Figure 1C] without later washout [Figure 1D] (negative enhancement relative to the normal liver).[3] Characteristic MRI imaging findings for FNH include isointensity or hyperintensity on 2-h delay gadobenatedimeglumine-enhanced MRI[2] [Figure 1E].

MRI

MRI was performed on a 1.5-T system (Excite™ HD, GE Healthcare, Milwaukee, WI)with an 8-channel phased-array torso coil. Imaging sequences included a breath-hold axial T1W dual fast gradient-recalled-echosequence (in-phase and out-of-phase sequences) (TR/TE, 150/2.3 and 4.5 msec; flip angle, 75°; field of view, 35×35 cm; matrix, 256×192; section thickness, 5-8 mm; intersection gap, 0 mm); a breath-hold axial T2W fast-recovery fast spin-echosequence with spectral fat saturation (TR/TE, 2600/90; echo-train length, 17; field of view, 35×35 cm; matrix, 256×160; section thickness, 5-7 mm; intersection gap, 1 mm; one signal acquired); a respiratory-triggered axial T2W single-shot fast spin-echo sequence with spectral fat saturation (TR/TE, infinite/180 msec; field of view, 35×35 cm; matrix, 256×192; section thickness, 5-7 mm; intersection gap, 0 mm); and breath-hold axial three-dimensional LAVA (liver acquisition with volume acceleration) dynamic T1W images with spectral fat saturation (TR/TE, 4.7/2.2 msec; field of view, 35×35 cm; matrix, 384×160; section thickness, 5 mm; intersection gap, 0 mm) at unenhanced, arterial (15-s delay), portalvenous (50-s delay), late portal venous (85-s delay), delayed (300-s delay), and late hepatobiliary specific phases (2-h delay). Gadobenatedimeglumine (MultiHance®, Bracco Imaging), 0.1 mmol/kg, was injected intravenously, followedby a saline flush.

Analysis

All MRI images were retrospectively reviewed by the author who measured the single largest transverse diameter of each FNH lesion and identified the presence or absence of interval increase in size. The measurement was performed on an arterial-phase image of a contrast-enhanced T1W sequence, by using a measurement tool in the PACS system (eFilm™, Merge Healthcare). A size increase or decrease of more than 10% of the initial diameter was considered to be interval growth or regression, respectively. To prevent miscalculation from technical differences, a size change of ≤10% was not considered as growth or regression. For lesions showing interval growth or regression, the differences in the diameters between the initial and last MRI examinations and the percentage increase or decrease of the initial diameter were calculated. The growth or regression rate was also calculated by dividing the difference of the diameters between the initial and last MRI examinations by the follow-up period. The initial size of the FNH was compared among growing, stable, and regressing FNH using the Student's *t*-test. In addition, the mean age of the patients and the mean interval between the initial and last MRI examinations were compared among the three groups using the Student's *t*-test. Statistical significance was defined as $P \leq 0.05$.

A chart review of all 120 patients was also performed to document the use of oral contraceptives during the follow-up period. The relationship between the use of oral contraceptives and the interval growth of FNH was evaluated using Fisher exact test.

Results

Among the 167 FNH lesions, 25/167 (15%) in 20 patients showed interval growth of FNH [Figure 2A-C] during the follow-up of 7-48 months (mean: 21 months). The interval

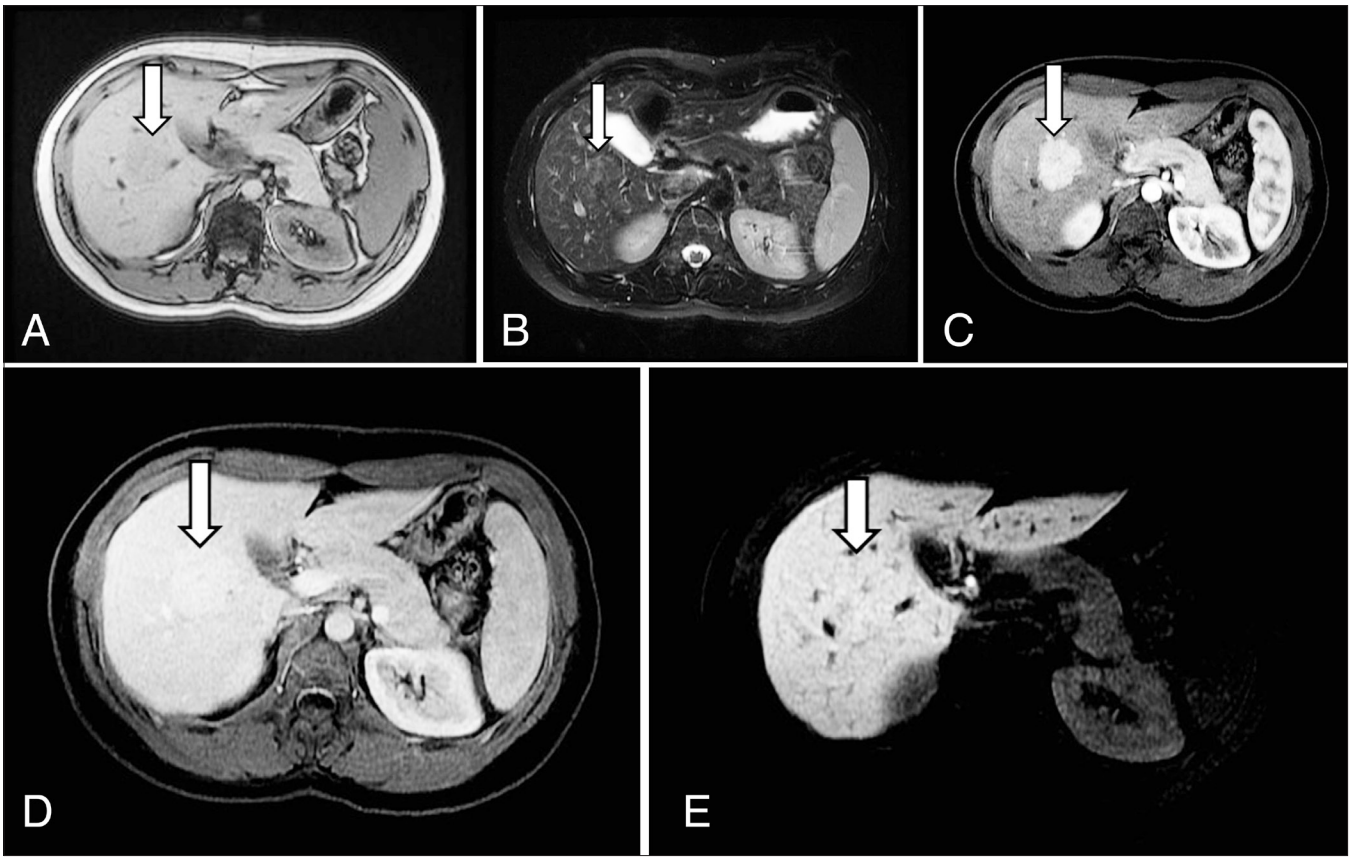

Figure 1 (A-E): Charicteristic imaging findings of FNH in a 47 year-old female. Axial T1W gadobenate dimeglumine–enhanced MRI (A) shows a slightly hypointense mass (arrow) relative to the liver. The T2W MRI (B) shows the mass isointense (arrow) with the adjacent liver parenchyma. Arterial-phase gadobenate dimeglumine–enhanced MRI (C) shows a homogenously enhancing mass (arrow). Portal venous phase MRI (D) shows the mass (arrow) to be mildly hyperintense relative to the liver with no wash-out. The mass (arrow) becomes isointense to the background liver in the hepatobiliary-specific phase (2-h delay) (E). These findings are consistent with FNH

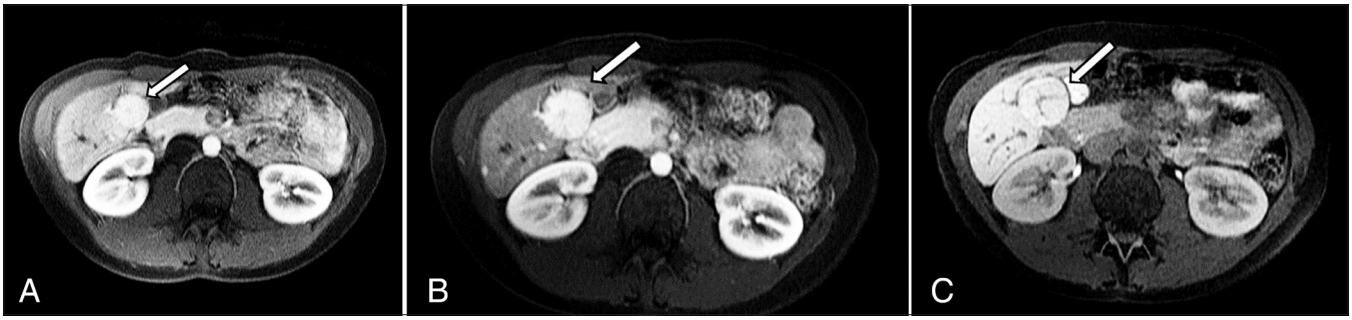

Figure 2 (A-C): Growing FNH in a 30-year-old female. Arterial-phase image of a gadobenate dimeglumine–enhanced MRI (A) shows a homogeneously enhancing mass (arrow) with a central nonenhancing scar. It measures 2.5 cm in its maximum dimension. Eighteen-month follow-up dimeglumine-enhanced MRI in the arterial phase (B) shows an interval increase in the size of the mass (arrow) to 3.1 cm. The mass (arrow) is slightly hyperintense relative to the liver in the hepatobiliary-specific phase (2-h delay) (C), with a central nonenhancing scar; the appearance is consistent with FNH

change in size ranged from 0.2 to 1.7 cm (mean: 0.6 cm) and interval percentage change in size ranged from 10.5% to 340% (mean: 64%). Growth rate was 0.003-0.141 cm/month (mean: 0.033 cm/month), with a percentage change of 0.34-14.6% (mean: 3.34%) per month. Thirteen of the 167 FNH lesions (8%) in 11 patients showed an interval regression during the follow-up of 7-63 months (mean: 22 months) [Figure 3A-C]. The interval change in size ranged from 0.2 to 0.9 cm (mean: 0.5 cm) and interval percentage change in size ranged from 10.4-60% (mean: 24%). The regression rate was 0.004-0.085 cm/month (mean: 0.019 cm/month), with a percentage change of 0.36-8.57% (mean: 1.9%) per month. The remaining 129/167 (77%) FNH lesions in 110 patients were stable in size during the follow-up period of

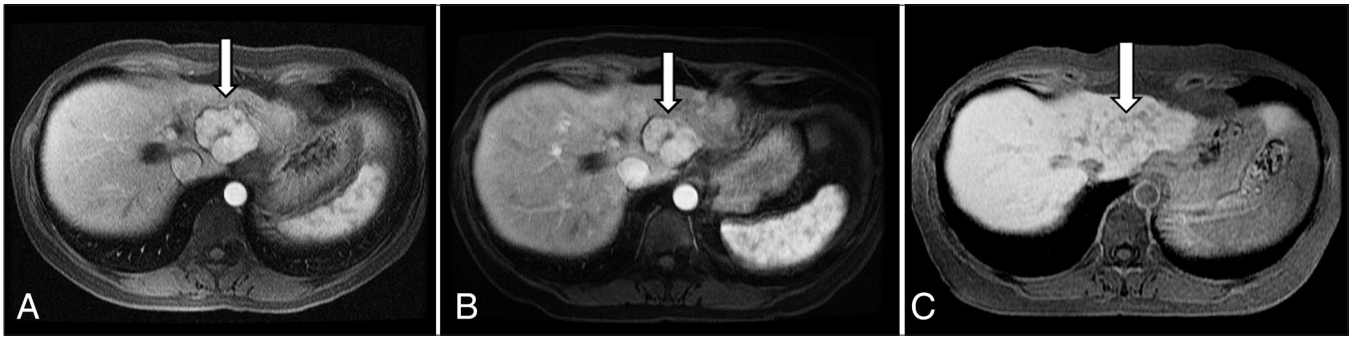

Figure 3 (A-C): Regressing FNH in a 54-year-old female. Arterial-phase image of gadobenate dimeglumine–enhanced MRI (A) shows a homogeneously enhancing mass (arrow), with a central nonenhancing scar. The mass measures 4.2 cm in its maximum dimension. Thirty-six-month follow-up dimeglumine-enhanced MRI in the arterial phase (B) shows an interval decrease in the size of the mass (arrow) to 3.4 cm. The mass (arrow) is isointense relative to the liver in the hepatobiliary-specific phase (2-h delay) (C), with a central nonenhancing scar; the appearance is consistent with FNH

6-64 months (mean: 19 months). Eighteen of 120 patients had multiple FNH lesions with different rates of interval change. There was no statistically significant difference in the follow-up periodsbetween the growing, regressing, and stable FNH groups (P>0.43).

The initial size of all FNH lesions ranged from 0.5 cm to 9.9 cm (mean: 3.3 cm). The initial size of the lesions was 0.5-7 cm (mean: 1.7±1.7 cm) in the growing FNH group, 0.8-9.9 cm (mean: 2.8±1.8 cm) in the stable FNH group, and 1.0-4.2 cm (mean: 2.3±1.2 cm) in the regressing FNH group. There was no statistically significant difference in the initial size among the three groups (P>0.06). The age of the patients ranged from 26 years to 61 years (mean: 43 years) in the growing FNH group, from 26 years to 54 years (mean: 44 years) in the regressing FNH group, and from 18 years to 80 years (mean: 45 years) in the stable FNH group. There was no statistically significant difference in the mean age between the three groups (P>0.39).

Only 5 of 17 (29%) women in the growing FNH group were on oral contraceptives, whereas 25 of 78 (32%) women with non-growing FNH were on oral contraceptives during the follow-up period. There was no statistically significant difference in the use of oral contraceptives between the two groups (P=0.83).

Discussion

There have been conflicting results regarding the natural history of FNH. Although the majority of the studies have shown that interval growth of FNH is extremely uncommon, there are occasional reports of FNH cases with interval regression.[7-10] The largest series is by Mathieu *et al*,[7] who followed 216 patients for 9 years and showed a size change of FNH in only 4/136 (3%). Three cases with interval regression and one with interval growth.

In our study, interval growth of FNH was seen in 20/120 patients (17%) and interval regression in 11/120 (9%). The incidence of growing FNH in our series of 120 cases was higher than in the study by Mathieu *et al*.[7] The reason for the difference is not clear. One possible explanation is the difference in the sizes of FNH between the two studies. In our study, the size of FNH at the time of detection was much smaller than in prior studies; the mean size of FNH in our study was 2.6 cm, while in the study of Mathieu *et al*[7] it was about 6cm.

FNH is believed to be a hyperplastic response to an underlying vascular insult.[1] It is reasonable to assume that FNH will grow in the early stages of development until it reaches its maximum size. Therefore, any interval growth of FNH will be more frequently observed if the lesion is first detected when it is small and is still growing. Recent advances in imaging techniques have enabled the detection of small incidental focal liver lesions and therefore there is a higher chance of observing a growing FNH.

The growth rate of FNH in our study was 0.003-0.141 cm/month (mean: 0.03 cm/month), with a percentage change of 0.34-14.16%/month (mean: 3.3%/month). This is much lower than the growth rate of HCC, which doubles in size at an average of 6.5 months according to the study by Ebara *et al*.[11] The slow growth rate of FNH can be one of the key features differentiating it from hepatic malignancy in these occasional cases of growing FNH.

Our study shows that there is no correlation between the interval growth of FNH and the use of oral contraceptives, suggesting that it is not necessary to discontinue oral contraceptives for patients with FNH. This result is in agreement with the studies by Mathieu *et al*[7] and Bonney *et al*.[12] In fact, FNH was first described long before the advent of oral contraceptives. Also, the incidence of FNH remained steady after the introduction of oral contraceptives in 1960, whereas there was a dramatic rise in the incidence of hepatic adenomas with the widespread use of oral

contraceptives.[13] Our study also showed that there was no significant difference in patient age among the three groups (growing, regressing, and stable FNH) at the time of diagnosis. The age distribution of growing and regressing FNH included a wide range, from young to middle age. It is noteworthy that none of the patients in this study group were symptomatic or had any complications throughout the follow-up period.

A limitation of this study is the lack of histologic confirmation of a large proportion of the FNH. We applied strict diagnostic criteria in cases without histologic proof, including characteristic findings of FNH on Gd-BOPTA-enhanced MRI.[3] Positive enhancement on the hepatobiliary-specific phase of Gd-BOPTA-enhanced MRI is known to be highly specific for FNH diagnosis.[2] Our review of the literature on FNH suggests that other researchers have encountered a substantial number of FNH lesions that were confirmed by imaging alone, without biopsy.[2,4,7,14] Moreover, histopathological diagnosis with a small biopsy sample obtained via percutaneous biopsy can also be challenging.[15]

Noninvasive imaging diagnosis of typical cases of FNH is now widely advocated[16] and it will not be reasonable or ethical to perform biopsy for FNH with characteristic MRI findings.

In summary, although FNH is benign and clinically non significant, in our study of 167 FNH cases, 17% of FNH showed interval growth and 9% showed interval regression.

References

1. Wanless IR, Mawdsley C, Adams R. On the pathogenesis of focal nodular hyperplasia of the liver. Hepatology 1985;5:1194-200.
2. Grazioli L, Morana G, Kirchin MA, Schneider G. Accurate differentiation of focal nodular hyperplasia from hepatic adenoma at gadobenate dimeglumine-enhanced MR imaging: Prospective study. Radiology 2005;236:166-77.
3. Hussain SM, Terkivatan T, Zondervan PE, Lanjouw E, de Rave S, Ijzermans JN, *et al.* Focal nodular hyperplasia: Findings at state-of-the-art MR imaging, US, CT, and pathologic analysis. Radiographics 2004;24:3-17.
4. Kim TK, Jang HJ, Burns PN, Murphy-Lavallee J, Wilson SR. Focal nodular hyperplasia and hepatic adenoma: Differentiation with low-mechanical-index contrast-enhanced sonography. AJR Am J Roentgenol 2008;190:58-66.
5. Dietrich CF, Schuessler G, Trojan J, Fellbaum C, Ignee A. Differentiation of focal nodular hyperplasia and hepatocellular adenoma by contrast-enhanced ultrasound. Br J Radiol 2005;78: 704-7.
6. Mathieu D, Bruneton JN, Drouillard J, Pointreau CC,Vasile N. Hepatic adenomas and focal nodular hyperplasia: Dynamic CT study. Radiology 1986;160:53-8.
7. Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, *et al.* Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology 2000;118:560-4.
8. Di Stasi M, Caturelli E, De Sio I, Salmi A, Buscarini E, Buscarini L. Natural history of focal nodular hyperplasia of the liver: An ultrasound study. J Clin Ultrasound 1996;24:345-50.
9. Ohmoto K, Honda T, Hirokawa M, Mitsui Y, Iguchi Y, Kuboki M, *et al.* Spontaneous regression of focal nodular hyperplasia of the liver. J Gastroenterol 2002;37:849-53.
10. Kuo YH, Wang JH, Lu SN, Hung CH, Wei YC, Hu TH, *et al.* Natural course of hepatic focal nodular hyperplasia: A long-term follow-up study with sonography. J Clin Ultrasound 2009;37:132-7.
11. Ebara M, Hatano R, Fukuda H, Yoshikawa M, Sugiura N, Saisho H. Natural course of small hepatocellular carcinoma with underlying cirrhosis. A study of 30 patients. Hepatogastroenterology 1998;45:1214-20.
12. Bonney GK, Gomez D, Al-Mukhtar A,Toogood GJ, Lodge JP, Prasad R. Indication for treatment and long-term outcome of focal nodular hyperplasia. HPB (Oxford) 2007;9:368-72.
13. Leconte I, Van Beers BE, Lacrosse M, Sempoux C, Jamart J, Materne R, *et al.* Focal nodular hyperplasia: Natural course observed with CT and MRI. J Comput Assist Tomogr 2000;24:61-6.
14. Quaia E, Calliada F, Bertolotto M,Rossi S, Garioni L, Rosa L, *et al.* Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: Diagnostic performance and confidence. Radiology 2004;232: 420-30.
15. Bioulac-Sage P, Balabaud C, Wanless IR. Diagnosis of focal nodular hyperplasia: Not so easy. Am J Surg Pathol 2001;25:1322-5.
16. Soresi M, Carroccio A, Campagna P, Riili A, Vaglica S, Terranova A, *et al.* Diagnosis of focal nodular hyperplasia. Role of imaging techniques. Ann Ital Med Int 2002;17:95-101.

Cite this article as: Halankar JA, Kim TK, Jang H, Khalili K, Masoom HA. Understanding the natural history of focal nodular hyperplasia in the liver with MRI. Indian J Radiol Imaging 2012;22:116-20.

Source of Support: Nil, **Conflict of Interest:** None declared.