Focal nodular hyperplasia of the liver in men: is presentation the same in men and women?

A Luciani, H Kobeiter, P Maison, D Cherqui, E-S Zafrani, D Dhumeaux, D Mathieu

Background: Focal nodular hyperplasia (FNH) of the liver is a benign hepatic lesion relatively common in women. No studies specifically designed to describe the presentation and imaging findings in males have been published.

Aims: The aims of this study were: (a) to describe the clinical and imaging findings in 18 men with FNH, and (b) to compare these data with those observed in 216 women with FNH observed during the same nine year period.

Patients and methods: According to a final diagnosis of FNH assessed either by pathological examination or by magnetic resonance (MR), the medical charts of 18 men with FNH observed at our institution were reviewed. In order to compare clinical and MR presentations, the files of 216 women with a total of 291 FNH lesions, investigated during the same nine year period, were reviewed.

Results: Eighteen FNH lesions, with a mean diameter of 37.5 mm, were demonstrated in the 18 male patients. A total of 291 FNH lesions with a mean diameter of 63.4 mm were comparatively demonstrated in 216 female patients. Mean age at diagnosis was significantly higher in men (p<0.01) and mean FNH size was significantly smaller in men (p<0.001). Surgery was more frequently performed in men (72.2%) than in women (16.7%) (p<0.001).

Conclusions: Our data indicate that FNH is rare in men and that the lesions are smaller and more often atypical than those in women.

PATIENTS AND METHODS

The medical charts of 18 men evaluated at our institution between July 1989 and July 1998 for FNH were reviewed retrospectively. The diagnosis of FNH was documented histologically in 13 patients; the five other patients met all of the strict MR imaging criteria for FNH (table 1). All 18 patients were referred to our MR unit for evaluation of a focal liver lesion discovered by ultrasound scanning. MR imaging was performed as reported elsewhere. MR images were reviewed by two experienced radiologists (HK and DM) who assessed the main diagnostic criteria (table 1) and measured the longest axial diameter of the lesion on the sequence showing the greatest contrast between the lesion and the surrounding liver. In the five non-surgically treated patients, follow up MR studies were performed, using the same protocol as initially, 2–9 years after the diagnosis (mean 3.8 years).

Clinical and MR imaging findings in 216 women with a total of 291 FNH lesions investigated at our institution during the same nine year period were reviewed by the same radiologists.

Statistical analysis

Patient age, maximum FNH diameter, and number of lesions per patient were compared in men and women using the Student’s t test. Fisher’s exact test was used to compare the proportions of patients who underwent surgical resection in the

Table 1 Combination of magnetic resonance criteria required for the diagnosis of focal nodular hyperplasia*

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Slightly hyperintense or isointense on T2 weighted images</td>
</tr>
<tr>
<td>Homogeneous signal intensity</td>
</tr>
<tr>
<td>Presence of a central stellate area hyperintense on T2 weighted images</td>
</tr>
<tr>
<td>Marked enhancement of the lesion at the arterial phase after injection of gadolinium chelates</td>
</tr>
<tr>
<td>Accumulation of gadolinium chelates within the central area on delayed contrast enhanced T1 weighted images</td>
</tr>
<tr>
<td>Absence of tumour capsule</td>
</tr>
</tbody>
</table>

*Data from Mathieu and colleagues.

Abbreviations: FNH, focal nodular hyperplasia; MR, magnetic resonance.
two populations. To determine whether diameter was different between men and women after adjustment for age, a linear regression model with age as an independent variable was constructed. A logistic regression model with age and FNH diameter as independent variables was used to determine whether sex independently influenced the likelihood of undergoing surgical resection. Analysis of variance with post hoc tests (Scheffe test) was performed to compare lesion diameter and number across age groups in the women. Because the variables were normally distributed, the arithmetic means (SD) are reported. All analyses were conducted using the SPSS (SPSS Inc, Chicago, Illinois, USA) for Windows package.

RESULTS

Eighteen FNH lesions with a mean diameter of 37.5 mm (range 25–70) were found in the 18 males (tables 2, 3). Mean age at diagnosis was 41.6 years (range 16–61) (table 2); 15 of the 18 patients (83.3%) were 30–50 years of age (table 3). No patient had a history of malignancy, cirrhosis, or drug abuse. Three patients reported upper abdominal pain (16.7%) and 15 patients (83.3%) were asymptomatic. Biochemical liver tests were normal in all but two patients (11.1%) who had 1.5–2-fold increases in serum gamma glutamyl transpeptidase activity. Fetoprotein level and hepatitis B and C virus serology were normal in all patients. On routine ultrasound scans, lesions were hypoechoic in five patients, hyperechoic in four, and isoechoic in nine. No Doppler quantitative analysis was available in this study. Each patient had a single FNH lesion; 13 lesions were in the right lobe, three in the left lobe, and two in the caudate lobe. Three patients (16.7%) had a solitary hemangioma.

MR findings met the criteria for FNH in 11 of 18 (61.1%) patients (tables 1, 2)). In six of these 11 patients, surgical resection was none the less performed at the patient’s request; in the other five, the size and MR features of the lesion remained unchanged during follow up, which was 2–9 years (mean 3.8). In seven of the 18 patients, one or more MR criteria were missing: central stellate area (two patients), heterogeneous signal intensity (four patients), and/or hypointense lesion on T2 weighted images (one patient). The lesion was removed surgically in these seven patients. Pathological examination of the specimens showed: (a) absence of macroscopic central stellate fibrous area within an otherwise typical FNH in the two patients in whom a central stellate area could not be seen on MR imaging; (b) haemorrhage and marked sinusoidal dilatation (two patients), or (c) areas of necrosis (two patients) in the four patients with a heterogeneous lesion; and (d) iron overload on Perls stained histological sections in the patient with a hypointense lesion on T2 weighted images.

In the 216 women investigated during the same period (tables 2, 3), mean age at diagnosis was 36.2 years (range 14–70). Seventy seven women reported upper abdominal pain (35.6%), 12 others had a palpable mass (5.6%), and the

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>41.6 (10.0)</td>
<td>36.2 (8.7)</td>
<td>**</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>37.5 (12.9)</td>
<td>63.4 (29.2)</td>
<td>**</td>
</tr>
<tr>
<td>No of FNH per patient</td>
<td>1</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Lesions with all MR criteria</td>
<td>11 (61.1%)</td>
<td>168 (77.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>13 (72.2%)</td>
<td>48 (22.2%)</td>
<td>***</td>
</tr>
</tbody>
</table>

FNH, focal nodular hyperplasia; MR, magnetic resonance.

**p<0.01; ***p<0.001.

### Table 3

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;20 years</th>
<th>20–30 years</th>
<th>30–40 years</th>
<th>&gt;40 years</th>
<th>&lt;20 years</th>
<th>20–30 years</th>
<th>30–40 years</th>
<th>&gt;40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>12</td>
<td>8</td>
<td>36</td>
<td>36</td>
<td>12</td>
<td>8</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Males</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
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<tr>
<td>n</td>
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<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>No of FNH per patient</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>
| None of the differences was significant.
remaining 127 patients (58.8%) were free of clinical manifestations. Fifty one women (23.6%) had 1.5–2-fold increases in serum gamma glutamyl transpeptidase activity, and the remaining patients had normal biochemical liver tests. The 216 women had a total of 291 FNH lesions (mean 1.3 per patient, range 1–12). Mean lesion diameter was 63.4 mm (range 10–180). The right lobe was more frequently involved (192 lesions in the right lobe versus 99 lesions). Table 3 shows the size and number of lesions by age group. MR findings were typical for FNH in 168 (77.8%) patients; atypical MR findings were disclosed in the remaining 48 patients including (a) absence of central area in 30 lesions, 15 of which had a diameter inferior to 20 mm, and (b) heterogeneous appearance in 18 lesions, related either to sinusoidal dilatation, haemorrhage, or steatosis on pathological examination. In these remaining 48 (22.2%) patients, histological confirmation of the diagnosis was made by biopsy obtained under laparoscopy using 14 gauge needles (36 patients) or by surgical resection (12 patients); in all 48 cases, histology confirmed the diagnosis of FNH. Fifty three haemangiomas were found in 35 (16.2%) of the 216 women.

Compared with women, mean age at diagnosis was significantly higher in men (p<0.01) and mean FNH size was significantly smaller (p<0.001) (table 2). Surgery was more often performed in men (72.2%) than in women (16.7%) (p<0.001). In the multivariate analysis performed to control for a potential confounding effect of age on the relation between FNH size and sex, FNH size was significantly smaller in men than in women (p<0.001). When both age and FNH diameter were controlled for, surgery was more often performed in men than in women (p<0.001).

Discussion

Whereas FNH of the liver is relatively common in women, particularly during the childbearing years, it is rare in men. In most published series, males contributed fewer than 15% of cases. To our knowledge, the clinical and imaging findings of FNH have not been compared in men and women. Our aim was to report salient clinical and MR findings in 18 men with FNH and to compare these data with those in 216 women investigated during the same period, using the same imaging protocol.

Our study confirmed that FNH is uncommon in men. During the same nine year period, 18 men, each with one FNH lesion, and 216 women with a total of 291 FNH lesions, were investigated at our unit, yielding a female to male ratio of 12.1, with men accounting for 8% of all patients. Because most of our study patients were outpatients referred to our teaching hospital MR unit after an abdominal ultrasound scan, we sought to determine whether the greater number of cases in women was ascribable to greater use of ultrasonography in women. We conducted a retrospective analysis over a one year period to assess the female to male ratio in patients undergoing hepatic and bile duct ultrasonography at a private radiology centre (table 4). Overall, 41.7% of the ultrason scans were done in men, 21.6% were done in patients younger than 50 years of age, and the female to male ratio varied across age groups from 4/1 to 1/1 (mean 1.4/1). Because the female to male ratio of FNH in our study was 12/1, these data suggest that recruitment bias related to differences in ultrasonography use between men and women does not explain the predominance of women among our patients with FNH.

Mean FNH diameter in our study was significantly smaller in men than in women (37.5 mm v 63.4 mm; p<0.001). Men had fewer lesions (1.0 v 1.3 per patient) although this difference was not significant. Several reports have suggested that FNH may occur in response to increased arterial flow caused by a vascular malformation. Female endogenous sex hormones have been implicated in the growth of FNH based on the following arguments: (a) in women, FNH is most common during the childbearing years; (b) mean age at FNH diagnosis is younger in women than in men; and (c) although the differences were not significant, we found trends toward a smaller diameter and a smaller number of FNH lesions in postmenopausal than in premenopausal women (table 3). A growth promoting effect of endogenous female sex hormones on FNH lesions could explain the differences in FNH lesion diameter and number found between men and women in our study. We recently reported that the number and size of FNH lesions were independent of the use of oral contraceptives of any type and for any duration. However, because oral contraceptives contain very low doses of oestrogens and/or progestagens, this finding is not evidence against enhancement of FNH growth by endogenous female sex hormones.

The MR features of FNH lesions were less often typical in men than in women (61.1% v 77.8%) although the differences were not significant. The two men with no centralstellate area on MR images had small lesions, 25 mm and 30 mm in diameter, respectively, with no central fibrous area on macroscopic examination of the operative specimen. The heterogeneous signal intensity seen in four other men was ascribed on histological examination to bleeding, sinusoidal dilatation, or focal necrosis. Finally, the low intensity signal from the lesion on T2 weighted images seen in another man was ascribed to iron deposits. Similar atypical findings have been reported in women.

Finally, surgical procedures were performed more frequently in men (72.2% v 22.2%). This can be ascribed to the larger proportion of atypical MR findings in men and to the greater risk of primary hepatocellular carcinoma in men. Our findings suggest that surgical resection should be avoided in men with typical MR criteria. Had this been the case in our male population, the number of surgical resections would have been reduced from 13 to seven. However, the number of men in our study was small, and multicentre studies in a larger number of patients are required to determine whether the conservative attitude validated in women is appropriate in men.
REFERENCES

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