Natural history of focal nodular hyperplasia
A retrospective study of 44 cases

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SUMMARY

Aim — To evaluate the natural course of focal nodular hyperplasia according to hormonal status.

Methods — Forty-four patients were included in this retrospective study. Tumor size was assessed with ultrasound examination. We studied the influence of hormone status on the course of the disease.

Results — All patients were women, the median age at diagnosis was 35 years and the median follow-up was 45 months. Ten patients were symptomatic at diagnosis, while none were symptomatic at the end of follow-up. The median size of the lesions was 56 mm. No complications occurred. The size of the tumor remained stable in 19 patients, increased in 12 and decreased in 13. Twenty-one of 37 patients stopped taking oral contraceptives: the lesion remained stable in 11 patients, increased in 3 and decreased in 7. Two patients didn’t stop taking oral contraceptives: the lesion increased in one, decreased in the other. Six patients became pregnant and 6 patients went into menopause during follow-up: the lesion remained stable in 3 and 4 patients respectively.

Conclusion — Focal nodular hyperplasia is a benign lesion. Tumor size remained stable in most cases. It seems that the hormonal status has little or no influence on the course of the disease.

Key words: Focal nodular hyperplasia. Benign tumor of the liver. Oral contraception. Pregnancy.

Natural history of focal nodular hyperplasia is an uncommon benign liver disease mainly observed in women with a prevalence of approximately 0.03% [1]. Until the eighties, diagnosis of focal nodular hyperplasia could not be formally confirmed preoperatively and most of the nodules were resected; probably also because the natural course of focal nodular hyperplasia was largely unknown [2]. Over the last ten to twenty years, progress in imaging, particularly magnetic resonance imaging (MRI), has made it possible to achieve nearly certain diagnosis before surgery in more than 70% of the cases [3, 4]. In addition, most patients with focal nodular hyperplasia are no longer operated on. Until one recent publication [5] there had been no information on the natural history of focal nodular hyperplasia so evidence-based recommendations could not be proposed for surveillance, particularly concerning the appropriateness of interrupting oral contraceptives [6]. The purpose of our work was to study the natural history of focal nodular hyperplasia and the influence of hormone status.

Patients and methods

Inclusion criteria in this retrospective study were the presence of one or more foci of nodular hyperplasia diagnosed more than one year before inclusion and absence of specific treatment (embolization, surgical resection).

Forty-four patients were included in the study population.

Diagnosis of focal nodular hyperplasia was based on MRI, using criteria reported in the literature [4] in 26 patients, and on pathology findings in 18 patients (ultrasound-guided biopsy in 17, surgical biopsy in 1).

MRI diagnostic criteria were: liver nodule with a homogeneous signal, iso-intense on T1- and T2-weighted sequences and high intensity signal of the central scar on T2-weighted sequences. Histological diagnosis was based on the presence of nodules composed of normal hepatocytes separated by fibrous septa containing thick-walled arteries, presence of angiocholic proliferation on the borders of the fibrosis without a normal interlobular biliary duct and minimal to moderate inflammatory infiltrate in the fibrosis [3, 5, 6]. Nodules were unique in 35 patients (79%) and multiple in 9 (21%). The following data were recorded at diagnosis: age, clinical signs, serum gGT, alkaline phosphatase, transaminases, hormone status. During follow-up the existence of clinical signs, development of complications, changes in hormone status (oral contraception, type, duration, pregnancy, menopause) were recorded. The size of the nodule was measured with ultrasonography. For patients with several nodules, the largest nodule was retained for analysis. Change in size of ± 10% was considered significant [9].

Results

Mean duration of follow-up was 45 months (range, 14-135).

Mean age at diagnosis was 35 years (range, 13-68).

General features

Ten patients presented moderate abdominal pain.

Liver tests were available at the time of diagnosis in 44 patients. They were normal in 23 (57.5%) and showed elevated
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Follow-up, respectively. Before diagnosis, 37 of the 44 patients were taking oral contraceptives regularly for a mean duration of 12 years (range, 4-22 years). Among the 23 women who were still taking oral contraceptives at diagnosis, 15 were using mini-dose pills and three women were on pills containing more than 40 µg ethinylestradiol. Twenty-one women interrupted their oral contraception at diagnosis while 2 continued to use a mini-dose pill. The evolution of nodule size is given in table II.

**Clinical and biological course**

There were no complications or deaths during the follow-up. None of the patients had developed clinical signs at last follow-up. Resolution of the clinical manifestations present in 10 patients at diagnosis was not correlated with changes in size of the nodule (unchanged 2/10, increased 4/10, decreased 4/10).

Liver tests were also performed in 27 patients (61%) during follow-up. Among the 23 patients with normal results initially, follow-up tests were available for 14 patients: liver tests remained normal for 12, while the nodule remained unchanged in 5, increased in 3 and decreased in 4. Modifications in liver blood tests were observed in two of the 14 patients: elevated gGT alone for one and concomitant elevation of gGT and transaminases for the other.

Among the 10 patients who had high gGT initially and who also had liver tests during follow-up, gGT remained unchanged in 4, increased in 3 and decreased in 3. There was no correlation with morphological data: e.g. for the 3 women whose gGT activity decreased, the nodule remained unchanged in 1, increased in size in 1 and decreased in size in 1.

**Ultrasound findings**

No new nodules were identified during the follow-up. The mean size of HNF was 56 mm (14 -118) at diagnosis. The size increased more than 10% in 12 patients (27%), remained unchanged in 19 (43%), decreased more than 10% in 13 (30%). We did not find any predictive value for age or size of the nodule at diagnosis (table I). There was no significant difference for age and size of the nodule at diagnosis for the different groups (table I).

**Hormone status**

Six women became pregnant during the follow-up at a mean 26 months (range: 5 - 43 months) after diagnosis. The size of the nodule increased by 40% during pregnancy in one woman, remained unchanged in 3 and decreased in 2. Mean size of the focal nodular hyperplasia was 50 mm (range, 30-66 mm) and 46 mm (range, 20-66 mm) at diagnosis and at last follow-up, respectively. Six patients were menopausal, more than one year before diagnosis in 4, one month before in 1, and 31 months after diagnosis in 1. Two patients were not taking hormone replacement therapy and one patient was taking subcutaneous estrogen therapy. Information was not available for the last two. None of the nodules increased in size, 4 remained unchanged, and 2 decreased in size. Mean size was 57 mm (range: 14-100 mm) and 49 mm (range: 14-97) at diagnosis and last follow-up, respectively. Before diagnosis, 37 of the 44 patients were taking oral contraceptives regularly for a mean duration of 12 years (range, 4-22 years). Among the 23 women who were still taking oral contraceptives at diagnosis, 15 were using mini-dose pills and three women were on pills containing more than 40 µg ethinylestradiol. Twenty-one women interrupted their oral contraception at diagnosis while 2 continued to use a mini-dose pill. The evolution of nodule size is given in table II.

**Discussion**

Since the development of imaging techniques enabling nearly 100% specificity for the diagnosis of focal nodular hyperplasia, most patients with this benign condition are treated surgically. Until recently, little information was available concerning the long-term course of focal nodular hyperplasia and the effect of hormone status and oral contraception. Recent studies [7, 9, 12] have demonstrated the benign course of non-reseted focal nodular hyperplasia. There were no complications in these three series reporting 128, 16 and 18 patients followed for 23 to 37 months, and the nodule remained stable in 50, 97, and 89% of the patients, respectively. In our population of 44 patients followed for nearly 4 years, the benign course of focal nodular hyperplasia was confirmed since no complications were observed. The reality of clinical manifestations related to focal nodular hyperplasia (basically pain) could even be questioned as no relationship between the course of the clinical signs and the size of the nodules could be demonstrated. The influence of hormone status on this condition predominantly observed in women is more difficult to establish. Three types of situations can be examined: pregnancy, use of oral contraceptives, menopause.

In our study, 6 pregnancies occurred during the follow-up. Five of the 6 nodules remained unchanged or decreased in size. Weinman et al. [10] and Mathieu et al. [11] found that focal nodular hyperplasia remained stable during pregnancy in 13 and 12 women, respectively. Only one case of an increase in nodule size has been reported [13] without clinical expression.

It is difficult to ascertain the effect of oral contraceptives on the evolution of HNF since 21 of the 23 patients taking oral contraceptives interrupted use at diagnosis. However, the fact that focal nodular hyperplasia decreased or increased in the 2 patients who continued oral contraceptives and the fact that the course of the nodules after interruption of oral contraception was very variable in the 21 women who discontinued suggests that low-dose estrogen oral contraceptives have little or no effect. Similar findings were reported by Mathieu et al. [7]. Among 89 women who had interrupted oral contraceptives at diagnosis of focal nodular hyperplasia, the nodule remained unchanged in 86, decreased in 2 and increased in 1. Among the 26 patients who were taking low-dose estrogen oral contraceptives after diagnosis, the nodule remained unchanged in 25, and in the last patient one of the two nodules disappeared.

Our population is the first where the effect of menopause on focal nodular hyperplasia can be assessed. Among the 6 menopausal women, the nodule remained unchanged in 4 and decreased in 2.

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**Table I. – Course of focal nodular hyperplasia by patient age and nodule size at diagnosis.**

<table>
<thead>
<tr>
<th>Oral contraceptives</th>
<th>Size of the nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Number of patients</td>
<td>12 (27 %)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31</td>
</tr>
<tr>
<td>Nodule size (mm)</td>
<td>43</td>
</tr>
</tbody>
</table>

**Table II. – Influence of oral contraceptives on the course of nodule size.**

<table>
<thead>
<tr>
<th>Oral contraceptives</th>
<th>Size of the nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Interrupted</td>
<td>3 (14 %)</td>
</tr>
<tr>
<td>Continued</td>
<td>1</td>
</tr>
</tbody>
</table>
We used ultrasonography to assess nodule size, similarly to Di Stasi et al. [9]. This technique is less precise than MRI, as employed by Mathieu et al. [7]. It has however been demonstrated that variation in size of ± 10% is significant at ultrasonography [9] and all the examinations in our population were performed by experienced operators.

In conclusion, focal nodular hyperplasia evolves little over time and in the majority of the cases remains asymptomatic. Routine surveillance is not be indicated if a certain diagnosis is achieved. In addition, hormone status appears to have little or no influence. There does not appear to be any contraindication for the administration of low-dose estrogen oral contraceptives.

REFERENCES