Focal Nodular Hyperplasia and Hepatic Adenoma: Epidemiology and Pathology

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Focal nodular hyperplasia • Hepatic adenoma • Hepatic tumor • Benign liver lesion

Abstract
Focal nodular hyperplasia (FNH) and hepatic adenoma (HA) represent the most frequent non-vascular benign liver tumors. They are often asymptomatic. The widespread use of high-resolution imaging modalities leads to an increase of incidental detection of FNH and HA. Physicians are thus increasingly confronted with these formerly rarely recognized conditions, stressing the need for concise but adequate information on the optimal clinical strategies for these patients. FNH is the most common non-vascular benign tumor of the liver. It probably arises as a polyclonal, hyperplastic response to a locally disturbed blood flow. It is typically found in asymptomatic women. Histologically, FNH can be described as a focal form of cirrhosis. Complications of FNH are extremely rare and surgical resection is generally not advised. HA is a rare monoclonal, but benign liver tumor primarily found in young females using estrogen-containing contraceptives. Although its exact etiology is unknown, a direct link between sex steroid exposure and the uncontrolled hepatocellular growth is suspected. Complications of HA are spontaneous bleeding and malignant transformation. Withdrawal of estrogen treatment and excision of large tumors (>5 cm) are established therapeutic strategies. In conclusion, although FNH and HA are reasonably well-described clinical and histopathological entities, their epidemiology and pathophysiology need to be further unraveled.

Introduction
Lesions in the liver demand a reliable diagnosis. The normal architecture of the solid organ can be disrupted by a variety of relatively harmless processes as well as a number of more serious pathological conditions. Deciding on the most adequate treatment requires a reliable diagnosis, and also demands good insight in the etiology of the disorder and its pathological behavior. Discrimination between malignant and non-malignant causes is crucial, but distinguishing between the various benign lesions is also important to choose an optimal therapeutic strategy.

Tumors of the liver often cause no or little symptoms, and a substantial part of these lesions is an incidental finding. The most common benign hepatic tumors cause complaints in about one third of patients, most often abdominal pain or right upper quadrant discomfort. Serum liver tests are mostly within reference ranges. In some cases, the radiological findings can lead to a diagnosis, while other benign liver lesions can only be exactly diag-
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Table 1. Epidemiology and pathology of focal nodular hyperplasia and hepatic adenoma

<table>
<thead>
<tr>
<th></th>
<th>Focal nodular hyperplasia</th>
<th>Hepatic adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical patient</strong></td>
<td>All ages 2nd to 5th decade</td>
<td></td>
</tr>
<tr>
<td><strong>Gender bias</strong></td>
<td>Female &gt; male</td>
<td>Nearly exclusively female</td>
</tr>
<tr>
<td><strong>Prevalence &gt;18 years</strong></td>
<td>4–30/1,000</td>
<td>Unreliable data, very low</td>
</tr>
<tr>
<td><strong>Prevalence &lt;18 years</strong></td>
<td>0.2/1,000</td>
<td>Unreliable data, very low</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>Asymptomatic</td>
<td>Abdominal pain or asymptomatic</td>
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<tr>
<td><strong>Laboratory</strong></td>
<td>Normal or non-remarkable</td>
<td>Normal or non-remarkable</td>
</tr>
<tr>
<td></td>
<td>Normal AFP</td>
<td>Normal AFP</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Spokes of wheel vascular pattern</td>
<td>Circular vascular pattern around lesion</td>
</tr>
<tr>
<td><strong>Pathological mechanism</strong></td>
<td>Hyperplastic reaction to vascular abnormality</td>
<td>Uncontrolled growth</td>
</tr>
<tr>
<td></td>
<td>Possibly estrogen-induced</td>
<td></td>
</tr>
<tr>
<td><strong>Histopathological features</strong></td>
<td>Central scar</td>
<td>Liver cell plates</td>
</tr>
<tr>
<td></td>
<td>Ductular reaction</td>
<td>No bile ducts (with the exception of ‘inflammatory type’)</td>
</tr>
<tr>
<td></td>
<td>Fibrosis</td>
<td>No fibrosis</td>
</tr>
<tr>
<td><strong>Mutation analysis</strong></td>
<td>Polyclonal</td>
<td>Monoclonal</td>
</tr>
<tr>
<td><strong>Gene expression</strong></td>
<td>β-Catenin pathway activation</td>
<td>HNF-1α inactivation</td>
</tr>
<tr>
<td></td>
<td>Ang-1/Ang-2 mRNA ratio elevated</td>
<td>β-Catenin pathway activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ang-1/Ang-2 mRNA ratio normal</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>None</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td><strong>Treatment of choice</strong></td>
<td>Classic FNH: expectative</td>
<td>Withdrawal of estrogen treatment</td>
</tr>
<tr>
<td></td>
<td>Diagnosis doubtful: consider excision</td>
<td>Excision/partial liver resection</td>
</tr>
</tbody>
</table>

nosed by pathological evaluation. On rare occasions even then a diagnosis cannot be made with certainty. This paper focuses on the differences and shared properties of focal nodular hyperplasia (FNH) and hepatic adenoma (HA) (table 1).

**Focal Nodular Hyperplasia**

The exact etiology of FNH is still incompletely understood. FNH generally does not cause complaints or require treatment, but an adequate evaluation of the lesion is indicated to discriminate it from other focal abnormalities in the liver.

**Pathophysiology**

FNH most probably arises as a reaction to local hemodynamic instability in the liver. The generally accepted theory on the genesis of FNH lesions is that arterial malformations disturb the local blood flow, thus causing a hyperplastic response of normal liver cells to either hypoperfusion or hypoxia [1]. As a hyperplastic adaptation is still responsive to growth control mechanisms, FNH is considered to be a truly benign condition and not expected to cause spontaneous bleeding complications or to undergo malignant transformation [2].

The notion that FNH lesions develop secondary to vascular abnormalities is supported by several observations. In some adults, the liver contains both hemangiomas and FNH. A study among 247 patients with hepatic masses identified 148 patients with FNH, of which 20% had concomitant hemangiomas of the liver, while in only 9% of patients with non-FNH lesions additional hemangiomas were identified [3]. Another indication is the different prevalence of FNH in families with hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant genetic disorder characterized by vascular malformations. In a study of 275 family members, FNH was found in 5 persons, all affected with HHT, bringing the prevalence among this group of HHT patients to 2.9% [4].
The putative role of vascular disturbances in the genesis of FNH is also supported by the observation of FNH-like lesions in patients with cirrhosis. In explanted livers of 130 cirrhotic patients, the presence of esophageal varices was significantly associated with the presence of FNH-like nodules, suggesting a contribution of portal hypertension to the formation of nodular hyperplastic lesions [5]. FNH lesions appear also to be associated with vascular malformations elsewhere, such as hemangioma and vascular malformation of the brainstem [1]. Recently, anecdotal evidence was published on the proposed sequence from hemangioma to FNH, probably starting with thrombosis of the hemangioma followed by involution of the lesion and subsequent occurrence of a hyperplastic regenerative reaction. A child that was analyzed at the age of 6 months for a palpable hemangioma of the liver presented 5 years later with a lesion of unknown origin in the same topographic area of the organ. Surgical excision and pathological examination revealed an FNH [6].

Patients treated for childhood malignancy in the past may be at particular risk for FNH. In a prospective cohort of 138 patients that received a hematopoietic stem cell graft at an age below 18 years, 17 FNH cases were identified, a median 6.4 years after the transplantation [7]. A French survey of 3,098 cases treated for any pediatric malignancy yielded 14 cases of FNH, a prevalence of 0.45%, which is still significantly higher than the previously reported prevalence rates in children [8].

Clinical Presentation and Diagnosis

Typically, FNH is an incidental finding in symptom-free patients. Abnormal serum liver tests provoking further diagnostic measures are reported in 12–13%. Levels of α-fetoprotein are within the normal range. Other symptoms are rare: palpable abdominal mass is found in 2–4% of patients, hepatomegaly and fever are observed in <1% of cases [9, 10].

MRI shows the highest sensitivity (~70%) and specificity (98–100%) for FNH, and as the majority of patients are women of childbearing potential, it is preferred to CT to avoid radiation exposure [11]. MRI reliably allows for discrimination between FNH and other focal liver lesions in most cases [12]. The imaging of FNH is discussed extensively by Van den Esschert et al. elsewhere in this edition [13]. Contrast-enhanced ultrasonography appears to be a valuable addition to the diagnostic toolbox, but its application is still limited to specialized centers [14, 15]. In young patients without any clinical or serological indications of hepatic disease, a liver biopsy is only done when imaging yields inconclusive results [16].

FNH is a truly benign condition, which justifies a conservative clinical approach. In symptomatic cases, resection of the lesion can be considered via open or laparoscopic surgery [17, 18].

Prevalence

FNH is the second most common benign hepatic tumor in adults, and third most common of all pediatric liver tumors. Epidemiological data on FNH are scarce. The few studies that report incidence and prevalence of FNH are not free of selection bias, stressing the need for additional high-quality multicenter studies.

In adults, FNH accounts for approximately 8% of all primary liver tumors, but again reports are limited. With an estimated rate of 2.25 per million children, the incidence of pediatric hepatic tumors is thought to be only a fraction of the numbers in the adult population [22]. A French group reported a prevalence of 0.02% in the general pediatric population based on the evaluation of 11,000 abdominal ultrasound examinations performed for other reasons, suggesting that actual prevalence may be higher [8]. FNH is the third most common benign hepatic neoplasm in children after hemangioma (14% of all liver tumors) and mesenchymal hamartoma (6%). HA accounts for another 2%, and liver teratoma forms <1% of all juvenile hepatic tumors [23].

The prevalence of FNH is higher in females, but the reported rates vary enormously. The female to male ratio of FNH is approximately 13–15:1 based on non-epidemiological studies, but ratios between 2 and 26:1 have been reported [3, 24, 25]. This makes FNH typically a condition found in females. In most adult patients, imaging studies reveal solitary lesions, predominantly of the right lobe, while in approximately 20%, 2–5 nodules are shown. Multiple nodular lesions (15–30) are present in only 3% of cases [3, 24]. Imaging may not reveal all microscopic lesions that can be found in histology though, indicating that these numbers may be an underestimation.

Pathology of Focal Nodular Hyperplasia

FNH can be divided into either classical (~70–80%) or non-classical (the remainder) lesions. Classical FNH is...
characterized by abnormal nodular architecture, malformed vessels and a proliferation of the small bile ducts (fig. 1a, b). This last property is by definition also found in non-classical FNH, but either of the other characteristics is absent or atypical, or cannot be confirmed with certainty. The non-classical group encompasses FNH with cytological atypia and the mixed hyperplastic and adenomatous FNH. Telangiectatic FNH used to be considered a non-classical form of FNH, but this ill-defined group is now considered a form of HA [26, 27].

Macroscopically, FNH resembles an aggregation of nodules of organized connective tissue and liver parenchyma, often with a lighter coloration than the surrounding normal liver tissue. The normal architecture is disturbed, with a disappearance of the normal regularity of portal areas and central veins. There is no surrounding capsule. Centrally in the lesion, a scar can often be recognized, from which fibrous septa with abnormal vasculature radiate towards the periphery of the lesion, but this cannot always be visualized prior to resection. In contrast to the situation in HA, the afferent artery supplies the cluster of vessels of various caliber from the central scar outwards, including tortuous arteries, capillaries, vascular channels of undetermined type and eventually the veins, a configuration that in some cases can be nicely seen using contrast ultrasound or CT [12].

Microscopically, the abnormalities can most adequately be summarized as ‘focal cirrhosis’: in the abnormal tissue there is a lymphoid and ductular reaction, the interlobular bile ducts have vanished, fibrous bands can be found and there is pronounced nodularity [27]. The nodular hyperplastic parenchyma is completely or incompletely surrounded by fibrous septa, and there can be an augmentation of the thickness of the hepatic plates to two or three cell rows, but the hepatocytes retain their normal phenotype [12].

**Molecular Pathology**

Paradis et al. [28, 29] concluded from their analyses that FNH lesions arise by polyclonal cell proliferation, unlike HA which is characterized by monoclonal expansion. Loss of heterozygosity was not found in FNH, and mutation analysis for the p53 gene and genes of the Wnt signaling pathway did not reveal any evidence for involvement of somatic mutations in the genesis of FNH [30]. This polyclonal origin further proves the benign nature of FNH and supports the strategy not to treat FNH in asymptomatic cases.

Gene expression data reveal an activation of the β-catenin pathway in FNH. β-Catenin is regarded as a pivotal stimulus for proliferation of hepatocytes, liver development and liver regeneration after injury. In FNH, β-catenin shows a heterogeneous distribution along the hepatocellular nodules in the absence of an activating mutation and in the absence of alterations in the Wnt signaling pathway [31].

Angiopoietins are regulatory molecules that control vascularization. Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) are regarded as counteracting molecules: while Ang-1 contributes to stabilization of vessel structures, Ang-2 is overexpressed at sites of vessel remodeling. A marked upregulation of Ang-1 and downregulation of Ang-2 was observed in FNH tissue [32]. The increased Ang-1/Ang-2 expression ratio could add to the

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Fig. 1. a, b FNH in a 47-year-old woman with prominent nodularity, fibrous bands containing tortuous arterial and venous vessels, and extensive lymphoid and ductular reaction.
formation of dystrophic vessels with thickened walls that are characteristic of FNH. A mouse model overexpressing the murine homolog of Ang-1, ANGPT1, shows abnormal and tortuous vessels resembling vascular alterations observed in FNH [32], but appears otherwise inappropriate as a model system for FNH [33].

In summary, FNH is considered a benign tumor of the liver, which probably arises in reaction to a real or erroneously perceived change in the local hemodynamic stability. Histologically, it can be described as a local form of cirrhosis, featuring fibrous septa, malformed vessels, and ductular proliferation. Asymptomatic cases should not be treated, while in symptomatic patients therapeutic actions should be carefully balanced against the expected gains and possible risks of treatment.

**Hepatic Adenoma**

HA is the third most common benign neoplasm of the adult liver next to hepatic hemangioma and FNH, but differs from the other two in the sense that it should be treated when reaching a certain size to avoid complications such as acute bleeding, and to prevent (rare) malignant transformation.

**Epidemiology**

HA is usually diagnosed in young females using oral contraceptives. Incidence and prevalence of HA are not exactly known. Reported rates in studies of limited size vary between 1 per million and 1%, the latter based on the finding of 1 case in a review of 95 routine autopsies, suggesting that the lower estimate will probably be more realistic [3, 19]. A 30- to 40-fold increase in the incidence of liver adenoma has been assumed in long-term users of oral contraceptives, with a base level incidence of 1 per million in women that used oral contraceptives for less than 24 months or not at all [34, 35].

HA is reported to be approximately 3–10 times less common than FNH [19, 20]. Only few cases in males have been described.

**Pathophysiology**

Most experts agree on the causal relationship between the administration of female and male sex hormones and the increased risk on developing HA. HAs were virtually unknown before the introduction of hormone-derived oral contraceptives in 1960. Since then, convincing evidence has been collected showing a dose-dependent and duration of exposure-dependent increase in the incidence of HA and adenoma size, although the exact disease mechanisms are still largely unknown. The reduction of estrogen content in contraceptives has possibly curbed the increasing incidence of HA in recent decades [35].

Other observations support the proposed role of sex hormones in the development of HAs. HAs have been described to occur after the use of exogenic male sex hormones, such as anabolic androgenic steroids by body builders [36], but also following androgenic steroid therapy for aplastic anemia [37]. There are also sporadic case reports of HAs in patients with elevated levels of endogenously produced androgens [38, 39] and sex hormone imbalance [40].

Glycogen storage disease is also positively correlated with the risk of HA. In the largest case series thus far the prevalence of hepatocellular adenoma was 50% among 27 young patients with type I glycogen storage disease, with 2–9 lesions found per patient. For type III glycogen storage disease, 4 out of 16 patients were diagnosed with HA, with lesion numbers ranging from 1 to 4 per liver. The exact pathophysiology of this association is not known. However, it is important to note that especially for type I glycogen storage disease the risk of malignant transformation of adenomas is markedly increased [41].

A special form of HA is the finding of multiple lesions, a condition designated as liver adenomatosis when more than 10 adenomas are found – a somewhat arbitrary cutoff. The etiology of hepatic adenomatosis is largely unknown, but there are good arguments to suppose a shared disease mechanism with HA [42]. Liver adenomatosis is often found in women with a history of oral estrogen exposure, suggesting that adenomatosis could be a more advanced form of HA. The regular histological finding of multiple lesions in partial liver resections performed for radiologically confirmed solitary HA is in line with that hypothesis.

**Clinical Presentation and Diagnosis**

Patients with HA are often asymptomatic. Large lesions may cause complaints, and in rare cases the patient presents with acute abdominal pain or shock after tumor rupture or hemorrhage. Abdominal discomfort is reported in 30–43%, and in a small subset (2–4%) of cases the tumor may be palpable. Abnormal serum liver tests are reported in up to 7% of cases [10, 43]. Serum tumor markers such as α-fetoprotein are in the normal range.

Diagnosis is often made by imaging studies, especially multiphase CT and MRI. Imaging of these lesions is discussed in this edition by Van den Esschert et al. [13]. Nee-
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Biopsies are controversially discussed, as these tumors are prone to bleeding and the amount of obtained material is often not sufficient to reliably confirm the diagnosis. Examination of the surgical excision preparation may be needed to make the distinction between HA and lesions with a similar presentation, such as FNH.

Major complications of HA include hemorrhage and malignant transformation. Hemorrhage due to spontaneous rupture has been reported in up to 30% of cases [44]. The potential risk of malignant transformation of HA was under debate for decades, but rates of 5% [44] in selected, well-characterized case series call for caution. Recent experimental evidence suggests that the pattern of genetic mutations in HA is of key importance for malignant transformation of HA (see below). Patients with large or multiple tumors are reported to be at risk for malignant transformation of these neoplasms, although the data available are limited.

Pathology of Hepatic Adenoma

Most HAs are reported to be solitary lesions on imaging (70–80% of cases), with tumor sizes ranging from <1 cm to well over 15–20 cm at the moment of detection. Archetypical hepatocellular adenomas are macroscopically formed of soft tissue, most often growing radially in the surrounding normal liver tissue. The lesion usually lacks an obvious fibrous capsule, which sometimes makes it difficult to recognize its borders. This feature also explains why hemorrhages occurring in the tumor mass may spread to the surrounding liver and even beyond, to the abdominal cavity.

Microscopically, HA typically shows little, if any, cytological atypia (fig. 2a). Cells are organized in liver cell plates of up to three layers, separated by sinusoids. The reticulin skeleton is mostly intact, and lesions lacking this reticulin layer should always be considered a well-differentiated hepatocellular carcinoma until proven otherwise.

As adenomas are only irrigated by peripheral arterial vessels and lack supply by the portal venous system, these sinusoids are similar to thin-walled capillaries. These aberrant vascular structures with extensive sinusoids and feeding arteries explain why adenomas are prone to bleeding. An additional characteristic finding is the absence of other portal tract elements: HA contains no bile ducts or ductular structures. This finding is pivotal in the discrimination between adenoma and FNH, which does feature bile ductules [27]. An important exception is the so-called inflammatory type adenoma, which can contain prominent ductular structures, but is now considered an adenoma subtype rather than FNH. Of course, the archetypical histology is not always found, and in some cases a conclusive diagnosis cannot be reached.

Molecular Pathology

Mutation analyses have enabled the development of subtype classification of hepatocellular adenoma. In particular, mutations in the genes of hepatocyte nuclear factor 1α (HNF-1α) in 40–50% of cases and β-catenin in <10% of cases appear to be relevant. Bioulac-Sage et al. [46] review in detail elsewhere in this edition the pro-
posed four subgroups [27, 45] for HAs based on the type of mutations detected, immunohistochemical staining patterns and histological findings. This classification allows the subtype characterization of 90–95% of HAs and permits a risk assessment for complications. Here, we only summarize characteristics of the HA subgroups, and refer to the dedicated paper of Bioulac-Sage et al. [46] for a more detailed description.

The largest group (35–50% of HAs) consists of tumors with inactivating mutations of the HNF-1α (TCF1) gene, and is characterized by steatosis. These adenomas usually lack cellular atypia and have no inflammatory infiltrate [45, 47, 48]. Bleeding is the most common complication of this tumor type.

Less common (10–18% of HAs) are tumors with an activating mutation in the β-catenin gene. These typically show cytological abnormalities in the absence of significant steatosis and may progress to hepatocellular carcinoma [27, 45, 47] or cause hemorrhage.

The third group (25–35% of HAs) consists of inflammatory or telangiectatic HAs and was formerly regarded as a subtype of FNH (fig. 2b). This group is histologically characterized by an inflammatory infiltrate and dilatation of the sinusoids. Often, convoluted ductular structures are found in areas that are reminiscent of portal tracts, but which lack the normal vasculature. The HNF-1α and β-catenin genes are not mutated. Still, the macroscopic features of these tumors resemble those of other HAs: they consist of easily bleeding soft tissue masses with little fibrosis rather than the compact nodular architecture characteristic of FNH. They also share molecular features with other types of HAs such as monoclonality and an unchanged Ang-1/Ang-2 ratio [28].

The fourth group (5–10% of HAs) cannot be attributed to any of the types mentioned above, and is considered as yet unspecified.

**Conclusions and Discussion**

Although FNH and HA are the most common non-vascular benign neoplasms of the liver, much is still unknown about their etiology and epidemiology. Typically, these lesions are diagnosed in females, suggesting a role for steroid sex hormones in the pathogenesis of both conditions, and most experts agree that oral contraceptive use is associated with an enhanced risk of HA. The introduction of oral contraceptives with lower hormone doses is thought to be responsible for the decreasing incidence of these hepatic lesions.

The limited number of systematic epidemiological studies makes estimates of incidence and prevalence of FNH unreliable, and of HA nearly impossible. Most reports are based on autopsy studies with limited subject numbers and are often single-center studies and thus prone to significant bias. A systematic registration of patients with proven FNH and HA in a multicenter setup would be needed to reliably describe the baseline incidence and prevalence of these benign liver lesions, and could add to a more elaborate identification of risk factors such as contraceptive use and a quantification of these effects.

Molecular genetics have improved the understanding of the pathophysiology of FNH and HA, but many aspects of these benign liver lesions are still enigmatic. The reported findings of monoclonality in HA and polyclonality in FNH fits well with the proposed disease mechanisms, but should be confirmed in larger cohorts of different origin. The group of benign lesions that cannot be classified by histological examination as either typical FNH or HA may need special attention and further molecular characterization in the near future. This would also allow to further optimize treatment strategies and to accelerate surgical interventions where necessary, but to avoid invasive modalities where not needed.
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